A REPORT OF PROCEEDINGS

OF THE 100TH
ANNIVERSARY
CELEBRATION
OF CHILDREN'S
HOSPITAL
MEDICAL CENTER
BOSTON
MASSACHUSETTS

TABLE OF CONTENTS

Page

FOREWORD
William W. Wolbach 2
MEDICINE FOR TOMORROW'S CHILDREN
Robert Q. Marston, M.D. 3
THE AFRICAN PRIMARY SCHOOL
Sir W. Arthur Lewis, Ph.D. 13
HEALTH PERSPECTIVES
Hon. Wilbur J. Cohen 25
SOME THOUGHTS ON PEDIATRICS OF TOMORROW
Sidney Farber, M.D. 33
VACCINES FOR VIRAL DISEASES OF CHILDREN – PAST, PRESENT, AND FUTURE
Wendell M. Stanley, Ph.D. 40
THE IMPACT OF IMMUNOLOGICAL PROGRESS
Gustav J. V. Nossal, Ph.D. 49
MOLECULES, GENES AND CHILD HEALTH
Edward L. Tatum, Ph.D. 58
THE CRITICAL ROLE OF ULTRASTRUCTURE
Betty Geren Uzman, M.D. 67
CEREBROSPINAL FLUID PHYSIOLOGY
Gordon V. Watters, M.D. 73
HEREDITARY ANGIONEUROTIC EDIMA
Fred S. Rosen, M.D. 80
THE CHOREIFORM MOVEMENTS
Peter H. Wolff, M.D. 83
THE DEVELOPMENT OF SKELETAL MALFORMATIONS
Arthur M. Pappas, M.D. 101
AN EXPERIMENTAL INTRACARDIAC INSTRUMENT
Walter J. Gamble, M.D. 109
TUMOR AND ENDOTHELIUM
M. Judah Folkman, M.D. 113
THE NEXT TWO DECADES
Leonard W. Cronkhite, Jr., M.D. 117
THE NATION'S NURSING NEEDS
Jessie M. Scott, R.N. 122

A

REPORT OF PROCEEDINGS

OF

THE 100th ANNIVERSARY CELEBRATION

THE CHILDREN'S HOSPITAL MEDICAL CENTER

Boston, Massachusetts

April 18 - 19, 1969

FOREWORD

The Children's Hospital Medical Center earlier this year celebrated its 100th Anniversary with activities at the Medical Center and the Sheraton-Boston Hotel. Included were several general sessions at which leaders in sociology and government, as well as medicine, presented papers of interest.

These papers are printed herein with the belief that the thoughts which were expressed may have some value in the future, and should be preserved for that possibility.

As the third oldest hospital for children in the United States, The Children's Hospital Medical Center has a long record of accomplishment. Its Staff and the work done by it have won well-deserved recognition throughout the world. Particularly in medicine, however, no man, no institution, stands alone. The contributions that have been made by the people of The Children's Hospital Medical Center could never have been possible were it not for other scientists and other institutions, both within the United States and abroad.

To those men and women – some of whom were with us at our centennial celebration – and to those institutions, The Children's Hospital Medical Center offers its most sincere thanks. With their continued collaboration and cooperation, Children's looks forward to a second century of service to children.

Boston, Massachusetts
July 8, 1969

William W. Wolbach
President

MEDICINE FOR TOMORROW'S CHILDREN: ON WHAT FOUNDATIONS CAN WE BUILD?

Robert Q. Marston, M.D.

Director, National Institutes of Health
U.S. Department of Health, Education and Welfare
Bethesda, Maryland.

For institutions, as for individuals, the observance of a centennial is a happy and exceptional occasion. It is a time to take stock of past accomplishments and to look to future opportunities. Measured beside much more aged institutions, such as the western European universities, a century might seem a rather modest milestone. But in this country, because of our youth, time has always had a different dimension. We have projected an image, both ridiculed and applauded, of a nation of people in a rush, leaping in with almost unbelievable energy and optimism to accomplish tasks that many would have thought impossible.

That spirit of optimism, of belief in our capacity to master difficult problems, characterizes the actions taken a hundred years ago in this city to establish what is today the Children's Hospital Medical Center, the largest children's hospital in the United States and next to the oldest.

The modest 30-bed hospital for children which young Dr. Francis Henry Brown started in 1869, four years after this country ended a long, bloody and agonizing civil war, was located on Rutland Street in Boston's South End. Twelve years later the hospital, with a staff of 12, moved to larger quarters on Huntington Avenue. We are told that patient costs at that time were $1.22 a day.

The present century has been one of steady growth, culminating in a modern medical center which treats 12,000 inpatients a year, and another 50,000 in outpatient specialty clinics, and contains the only school of nursing affiliated with a pediatric hospital.

Children's has exerted a pioneering influence in a number of fields. It was the first, for example, to set up an Adolescent's Unit to supply medical care to teen-age patients in facilities geared to meet their special needs. It operates the largest cystic fibrosis clinic in the world, one of the largest cerebral palsy clinics in the country, and the first PKU clinic in the United States.

The influence of this institution extends far beyond the city of Boston and the region it serves. Through its research and teaching programs, Children's is a national resource for the improvement of medical care and the training of manpower on a broad front.

No pediatric hospital, for example, has done more to advance the concept of total care for cancer patients than Children's. The success of this program, as well as the pioneering role of Dr. Sidney Farber and his associates in the chemotherapy of childhood leukemia, are evident in the close relationship between the institution and the practicing physicians who look to it as a major resource for diagnostic assistance and referral.

The same can be said of Children's blood research center, which under Dr. Louis K. Diamond, has become a teaching resource for the entire Nation. One could extend the list almost indefinitely – Enders in the viral diseases, Shwachman in cystic fibrosis, Gross in surgery and many others equally outstanding in their fields.

But beyond the advances that identify Children's as one of the Nations's great pediatric centers is something less tangible, something less susceptible to measurement. It is the example of an institution that has successfully served its community. The history of Children's is a record of devoted service by all the health professions and by the community at large. In an age when our cities are struggling desperately with problems that seem at times almost insurmountable, we need the example of success, the proof that problems are in fact soluble and that the democratic processes of persuasion and conciliation still work.

As we look forward to tomorrow, the prospect of further scientific advancement, supported by a perceptive and compassionate citizenry, encourages optimism. President Nixon summarized his view of a future enriched by science and technology in these words:

> Science has served mankind faithfully and well. It has dramatically extended the average lifetime, shortened geographical distances, increased industrial productivity, reduced poverty, and in the long trial of war, contributed significantly to the cause of freedom. . . .
>
> If science and technology were to founder or stagnate, many of our hopes would collapse. To the extent that we neglect this source of our greatness, and to the extent that we fail to preserve the conditions of openness and order that made our progress possible, we are living off the land of civilization without refertilizing it. . . .
>
> Instead, we must bring about a new dawn of scientific freedom and progress. As the world's investment in science expands, the impact of technological progress will be more profound. . . .
>
> In 20 years the world may be as enormously different from today as [today] is different from 1900.

The experience of Children's Hospital during the last century recapitulates to a considerable extent the history of the best of pediatrics. It is not necessary for me to specify further for this audience the numerous examples of the growing impact of science on practice; the constant ebb and flow of hope, expectation and frustration which are characteristic of the sick and those who care for the sick; and the impact of societal changes, of which there have been so many since 1869 as this Nation and the world passed through numerous major crises. We do have firm foundations in many areas on which we can build for the future, but there are also uncertainties.

Listen, for instance, to John Russell of the Markle Foundation as he talks about the problems of an institution in keeping a focus on its objectives.

> As shot after shot rang out, as Washington burned, as work in universities

> came to a halt, to continue an "ordinary" program and to act as if nothing had happened might appear to be completely heartless and thoroughly stupid. And yet in spite of the daily headlines this Foundation did precisely that. We deliberately tried to "keep our cool," as we have many times in the past during national emotional crises. We have always believed this to be the duty of a free foundation – and by a free foundation we mean one with a broad charter, unhampered by the donor's restrictions, with an intelligent and experienced board of trustees generally unmoved by emotional appeals. Unhampered and unmoved, such a foundation has the privilege, really the duty, of keeping its head and helping to maintain those services so essential to our civilization, such as it is, looking forward to a better day ahead.
>
> This foundation has weathered many such storms during its brief history. One came with World War II. Another came with the Korean war, and on that occasion we consulted many individuals, nearly all of whom urged the foundation maintain a "business-as-usual" policy as long as that was at all possible, on the ground that medical training and research must be maintained regardless of war. We have found this to be the present point of view even though the emotions stirred up at the moment are more intense. It's pleasing to know that so many approved our position even though we are all sick at heart. It's not easy to remain cool these hot nights.

This example of a small successful foundation in the health field, agonizing about the relationship of its past to its future, is indeed symptomatic of the main theme of your centennial exercise, focussing as it does on the next century in pediatrics. But there is a more important reason for my choosing this quotation as I turn from the consideration of your accomplishments to a consideration of the future.

Let me reread the last words: ". . .though we are all sick at heart. It's not easy to remain cool these hot nights."

How many in Boston in 1869 must have had similar feelings? How many must have sensed an almost overwhelming desire to bind up the Nation's wounds quickly at all costs? What little experience on which to choose the building blocks! for it was a new world and an uncertain world in which the age-old problems of man were close to the consciousness of everyone – ignorance, poverty, war, disease. But would anyone in Boston in 1969 suggest that our concern for these ancient enemies are less intense today?

As I look to the future, it seems to me that these constant companions of mankind will continue to ride our coattails for a long time to come. And we are moving into a new world – a world in which past experience, while pertinent and relevant in some areas, is unlikely to be pertinent or relevant in others. It is the exploration of this concept on which I would like to spend the rest of my time this evening.

Let me start by quoting Dr. Margaret Mead.

> The young people who are rebelling all around the world, rebelling against whatever form the governmental and educational systems take, are like the first generation born in a new country listening to their parents' tales of the old country and watching their parents grapple, often clumsily, often unsuccessfully, with the new conditions. They have no firsthand knowledge of the way their parents lived far across the seas, of how differently wood responded to tools, or land to the hoe. They see the tasks which their unaccustomed elders are performing as poorly done; they feel that there must be a better way, and that they must find it.
>
> For now, nowhere in the whole world are there any elders who know what the children know, no matter how remote and simple the societies in which the children live.
>
> All of us who grew up before the war are immigrants in time, immigrants from an earlier world, living in an age essentially different from anything we knew before. We still hold the seats of power and command the resources and the skills which have been used in the past to keep order and organize large societies.
>
> The elders are separated from the young by the fact that they too are a strangely isolated generation. No generation has ever known, experienced, and incorporated such rapid changes, watched the sources of power, the means of communication, the definition of humanity, the limits of their explorable universe, the certainties of a known and limited world, the fundamental imperatives of life and death – all change before their eyes. They know more about change than any generation has ever known and so stand, over, against, and vastly alienated from the young, who, by the very nature of their position, have had to reject their elders' past.
>
> As long as any adult thinks that he, like the parents and teachers of old, can become introspective, invoke his own youth to understand the youth before him, he is lost. But once the fact of a deep, new, unprecedented, worldwide generation gap is firmly established, in the minds of both the young and the old, communication can be established again.

Even if true, you may say, what does this imply for medicine – essentially a science? Our future is dependent upon an orderly and painstaking accumulation and expansion of knowledge. We are not subject to the type of discontinuity that Dr. Mead describes, where a nation or a world changes direction so rapidly that almost all past experience becomes suspect.

But my answer is yes and no. While it is true in general that the forward march of understanding in the biomedical area has been characterized to date by the accumulation of a large amount of information which, when synthesized, leads to relatively limited increases in understanding, it seems to me unlikely that this will continue to be so over the next century. We may hope for the development of generalizable theories concerning life processes comparable to the quantum theory or other concepts from the physical science field.

How realistic is such a hope, and from what type of investment in human resources is it most likely to flow and what would be the impact? The latter question is the easiest to answer. Immediately the need is eliminated for the detailed, step-by-step filling in of a gigantic, complex jigsaw puzzle, and the emphasis shifts to the design of experiments to test further and to amplify the generalized concept. Research would tend to become more abstract, more theoretical, and the application of the findings more predictable.

Perhaps of greatest importance would be the change in attitude of people in the health fields. And here it seems to me that we do have considerable experience, particularly from the impressive advances of even the last two decades. The advent of the antibiotics age, with penicillin, did indeed change our way of thinking about illness, as well as raise new ethical and moral problems. The who-shall-live and who-shall-die questions was a very real one during the early days of scarce supplies.

I started in medical school before the availability of penicillin and streptomycin, participated as a student in the first successful treatment of a patient with generalized peritonitis, in Richmond, and then spent two years in the laboratory of Lord Florey (or Sir Howard as we knew him then) just as the work on penicillin was being concluded as an activity there. As a result, I was keenly aware that the universe of infectious diseases in the early forties became almost irrelevant to the needs of the late forties. Medical practice, public expectation, and our attitude towards disease had changed overnight.

The second question – where is one most likely to see the emergence of generalizable theories of life processes – can only be guessed at. Surely we are all impressed today with the excitement in genetics – the understanding of DNA and even the photographing of it – the recent reports of the synthesis of an enzyme, and the analysis of the antibody molecule. In Institute after Institute at NIH, one senses the excitement of our own scientists and in the field at large.

Almost every line of research presents its broader implications. There are the various relationships in cancer as an approach to human biology, the use of L-Dopa in Parkinsonism as a key to better understanding of the nervous system, the effects of interferon on viral infections as related to the basic mechanism of RNA-cell reactions, the understanding of the reproductive process as related to the world's population problems, the concern with multiple low-level environmental contaminants on neonatal development – to name only a few.

In pediatrics, happily, the common childhood diseases are approaching extinction, and it is probably safe to predict that they will be virtually eradicated within 10 years. So the field of pediatrics as we have known it, with its emphasis on the common infections, preventive inoculations, nutritional and digestive disorders, and congenital defects resulting from infection of the mother during pregnancy, will cease to exist, say in the 1980's.

On the other hand, a broader view of pediatrics, encompassing child development throughout the perinatal period and beyond, reveals a field with remarkable capacity for growth. Here, there is a special need for the type of broad, sound, generalizable concept of the basic nature of man which we must develop in the future.

Thus, with a little imagination, one can visualize a hospital for tomorrow's child. One major department will provide genetic counselling for prospective parents. This service is already available, of course, in regard to certain known disorders in the family. As genetic knowledge and predictability advance, such a service will become more useful. It is feasible that eventually a precise "genetic profile" of the parents could be prepared (using tests yet to be devised) for computing the probabilities that the offspring will inherit certain conditions, adverse or otherwise.

Working closely with the genetic counselling department will be that branch of pediatrics concerned with the prevention of defects. Might we speak of "orthogestation?" An example in experimental practice today is the study of amniotic fluid withdrawan during pregnancy, particularly in regard to erythroblastosis fetalis.

The potentialities of this technique are indicated by a recent study on Lesch-Nyhan disease, first described by an NIH-supported investigator in 1964. This rare disease is characterized by brain damage, a compulsion to chew away the lips and fingers, excessive production of uric acid, and an early death. In 1967 Dr. J.E. Seegmiller, heading an NIH team at Bethesda, showed that Lesch-Nyhan patients are all males and are deficient in an enzyme of purine metabolism, PRTase,* as a result of a mutant gene on the X chromosome. The same scientists have now identified an unborn female child as a carrier of the trait by measuring PRTase activity in cultures of cells obtained from amniotic fluid of the mother, a known carrier. The same general procedure is believed capable of detecting a fetus fully afflicted with this or other hereditary metabolic disorders at an early stage.

We are drawing even farther from the idea of heredity as inevitability. It is an established tenet of genetics that one does not, strictly speaking, inherit genetic characters, but only a susceptibility to them – that appropriate modification of the immediate environment in which a gene is operative could prevent or alter its expression. Stated otherwise, genes determine susceptibility to character formation. The effective environment for the formation of a character such as hair color, height, color blindness, or susceptibility to cancer may include intrauterine factors, diet, occupational influences – any condition, in fact, to which the individual is exposed; and it may include, secondarily, physiologic factors affecting cells. Thus the adverse environment, whether that of the individual or a susceptible cell, is not beyond control. Without overlooking the exceptions – the effects of totally absent genes and chromosomes, for example – the possibilities that might be opened by a research breakthrough in "orthogestation" are staggering.

---

*Hypoxanthine-guanine phosphoribosyltransferase.

Such thoughts lead inescapably to the possibilities of genetic engineering – "family planning" in a genetic sense. Certainly, all this carries us far beyond pediatrics as we know it today, but it can be viewed as within the framework of that field. As to the ethical implications, I agree with Dr. Philip Handler's statement at the recent Westinghouse Talent Search Award Dinner, that we should prepare now for the day when genetic engineering will be possible. Let us not underestimate the impact when this capability becomes available.

A rather large department of our future children's hospital will be concerned with child development; for it will be possible to alter growth and morphology in many meaningful ways. Control over child development may prove an effective approach to preventing or delaying degenerative diseases of the later years. Indeed, "pediatrics-geriatrics" may emerge as an important subdiscipline.

A suggestion of the content of such a field is given by the recent observations of two NIH grantees, Drs. Jules Hirsch and Jerome L. Knittle of Rockefeller University.* They found that early nutritional factors such as overfeeding, in both animals and humans, can produce severe obesity by permanently increasing the number of fat cells. These cells were more abundant in adults who had been fat for a long time, and weight reduction did not diminish the number. On the other hand, prison volunteers who became obese experimentally showed an increase in fat-cell size but not number. The number of fat cells appears to be established before adulthood.

Dr. Hirsch and associates, in further studies, found that the large fat cells associated with obesity have a diminished sensitivity to insulin, and that weight loss both decreases the cell size and brings plasma insulin levels to normal.

For "pediatric-geriatrics," the implications of these studies are, of course, weight reduction in childhood as a means of preventing intractable obesity – and associated disorders – in later years.

The expanded role of the pediatrician in child development will call for a much broader background in psychology and sociology. Training will seek to correct present deficiencies in community medicine through greater emphasis on processes of learning, development, behavior. The practitioner will have to be more knowledgeable about his patient's social background; will have to relinquish some time-consuming mechanical functions, like the taking of histories and the giving of injections; will need a broader scientific base; and will have to know a great deal as yet unknown about the mother.

---

*See *Highlights of Progress in Research,* NIH, 1968, and *Weekly Report to the Surgeon General,* March 12, 1968.

The field of pediatrics will continue to be popular with women physicians. A recent analysis of trainees under NIH training grants in 1967 showed that 20 percent of 353 trainees seeking or holding an M.D. in pediatrics were women, as compared with only 10 percent in over-all clinical medicine. For the Nation as a whole, about 3000, or 18 percent, of active women physicians were specializing in pediatrics in 1965.* These and earlier data (1953) showing about the same percentage indicate that pediatrics remains the most popular specialty among women in medicine.**

So far, we have been looking ahead to what is often called the "foreseeable" future – time that one can predict with relative confidence. If we attempt, now, to look ahead a century, the crystal ball grows dimmer and only the barest outlines are discernible. There is still a Children's Hospital and it is playing an important role in pediatrics. Through genetic engineering and highly specific prenatal care, the birth of an unwell child is a rarity. But the problem of keeping him well in an extremely complex environment is a tremendous responsibility, drawing upon knowledge yet unforeseeable about human society and the physical setting. Surely, pediatrics as we know it today will have long ago ceased to exist. But the pediatrician will be one of the principal agents in helping every child attain not only health and long life, but also his full potential as an individual.

But for the immediate future, let me return to the difficult question, the implied premise in my title – On what foundations can we build? or, as I stated it later, Where should we put our resources?

Margaret Mead said, "Our past experience may not be pertinent to future needs." Harvard, even Harvard – next door and, I probably should say, all around us – is struggling with that very question. But John Russell has said that the training of physicians was such an essential service that, even during a period of terrible strife, it was decided to continue to have "an ordinary program." In our own troubled times, Children's Hospital has continued to cover the spectrum from basic research to community service.

Yes, the problems of war, poverty, ignorance and disease are as much on our minds today as they were in 1869. Against this background, it seems to me that the highest priority of this venerable institution, of this Nation, and perhaps of mankind, is to do those things necessary to hasten the development of generalizable theories for illuminating life processes.

We are far along the way. Twenty years ago, the concept that a child with acute leukemia could live for a year was as remote as man's reaching the moon. Tomorrow the question of how far man can reach for the stars in his human aspirations will no more depend on therapies ministered in a piecemeal fashion to each individual ill of mankind than his ability to reach the stars in a spaceship will depend on the counting of each molecule in the atmosphere. Thus, we must push forward, with an optimism and enthusiasm characteristic of this Nation, to understand the processes of life and disease as soon as possible. Let it not be said a hundred years from today that we lacked the courage or conviction of our forefathers, or that the essential limitation was a failure to commit our resources.

---

*The Fuller Utilization of the Woman Physician, p. 73. Report of a conference sponsored by American Medical Women's Association, etc.; Washington, 1968.

**Survey of Women Physicians Graduating from Medical School 1925-1940. Roscoe A. Dykman and John M. Stalnaker. *J. of Med. Ed.* 32, vol. 3, part 2, pp. 3-38, March 1957.

THE AFRICAN PRIMARY SCHOOL
IN ITS
ECONOMIC CONTEXT

Sir W. Arthur Lewis, Ph.D.

Professor of Economics and International Affairs
Princeton University, Princeton, N. J.

The right to schooling is one of the fundamental rights of children. One does not have to elaborate why this is so. The human race is distinguished from the rest of the animal kingdom by our capacity to read and write and count; to store information; to communicate over long distances, and over the centuries. Nobody questions any more that every child should be in school, if this is feasible.

One has to add the qualification "if this is feasible" because it is not always feasible, especially in Africa, to which I am confining myself in this paper. African leaders came to power in the 1950's and 60's with universal primary education as their highest priority. The imperial powers had provided schooling for only 5 to 20 per cent of African children, and this had been an important part of the nationalist case against them. As soon as the Africans got into power they started to build more primary schools.

They ran at once into two problems, the problem of tempo, and the problem of cost.

Suppose one could afford to put all the children in school, how many years should one take to get from 20 to 100 per cent? Essentially this is a problem of teacher quality. It takes time to train good teachers, and more time still to train those who are to train the teachers. If one emphasises quality, and insists on appointing only trained teachers, the operation is likely to take half a century more or less, especially when you remember that in these high birth rate countries the number of children itself doubles every 30 years. There is a strong case for insisting on quality. The quality of one's universities depends on the quality of the secondary schools, which in turn depends on the quality of the primary schools. If you suddenly decide to flood the country with low grade primary schools you pull down the quality of the whole educational system for a couple of generations.

But the case against insisting on quality is equally good. If some schooling is better than no schooling, children should not be deprived of school merely because the teachers have not been to training college. The African leaders were influenced by this argument, and expanded the primary schools rapidly, hiring whomsoever they could as teachers. As for the quality of secondary and university education, they tried to maintain this by having at each level schools of different quality, including some highly selective ones, so that some schools of high quality were retained. This was not so easy to do politically, since in these democratic days the right of a school to admit only those students who meet its high entry standards is being challenged everywhere, and even in the United States some prestigious institutions have felt themselves forced into lowering their standards of admission. But so far the Africans have succeeded better than, say, the Asians in grappling with this problem, and have managed to retain some first-class schools despite the sudden flood of students.

The quality problem could therefore be handled; the cost problem was more formidable. This problem is composed of two elements. One is that the proportion of children is one and a half times as high in a high birth rate country as in a low birth rate country. It therefore takes proportionately 50 per cent more of the national income to have universal primary education. Beyond this, the salaries of African teachers are high relatively to national income. In the United States the salary of a primary school teacher is between 1½ times and twice the per capita income of the country; whereas in Africa the salary of a primary school teacher, even if it were as low as $500 U.S. per year, would still be 6 times the per capita income. When one puts these two elements together, the result is that whereas the United States can pay for primary education with taxes equivalent to about one per cent of national income, the same number of years of universal primary education, with the same staff-student ratios, would cost an African country 5 per cent of the national income in taxes. Add the costs of secondary, higher and technical education, and education alone would eat up more than half the tax revenue of these governments.

Why do the teachers cost so much? Five hundred dollars a year is not a lot of money in any absolute sense, even when one allows for the lower costs of food and housing. It is a lot of money only when compared with the incomes of the farmers. But, of course, since it is the farmers who have to pay the taxes, this is the comparison we have to make. Our question then becomes, why does an African teacher earn so much more than an African farmer, whereas – at least in the North – an American teacher earns the same or less than an American farmer?

The answer is in the very situation which we are trying to remedy, namely, the shortage of educated persons. In a community where only 10 per cent of children complete primary school and there are hardly any secondary schools, there is a premium on the services of primary school leavers. They get the white collar jobs which otherwise would go the the graduates of secondary schools; they become primary school teachers, typists, bookkeepers, clerks, and so on. So a high standard of earnings is established even for primary school graduates. Moreover, in these African communities the shortage of middle and higher educated was met, under the imperial powers, not by training Africans for these jobs, but by bringing in French and English men and women in considerable numbers for middle and upper occupations. These inportees had to be paid more than they could have earned at similar jobs in England or France. So Africa acquired a wage and salary structure which is fantastically distorted; more unequal than anywhere else in the world. This affects not only education but also any other service which you try to provide in Africa, such as medical service, and it affects also the costs of manufacturing industry relatively to the farmers' incomes. One simply cannot provide services in Africa on a similar scale to other continents because services cost so much.

This is a temporary phenomenon, which strengthens the case for multiplying the number of educated as rapidly as one can, so as to bring down their relative earnings, even if multiplication means some fall in average standards. From the economist's view this is the simple and obvious solution; but from the politician's view it is not so simple. Nobody likes to have his earnings brought down, even relatively. In the Western world this has been happening to the middle classes throughout the twentieth century. At the beginning of this century the wife of a professional man, such as an economist, had at least one servant, and possibly two. Nowadays only doctors' wives can afford to have servants. This narrowing of the gap in earnings between the bottom and the top has everywhere produced discontent and grumbling in the middle classes, which has in some places resulted in middle class movements of a Fascist character. The problem is the same in Africa. There the educated at every level, from primary to the top, have been much disturbed by what is happening to their relative economic distance as the mumber of educated grows so swiftly, and the resistances which they offer, especially through trade union and professional associations, have had to be faced. Everywhere now in Africa the politicians and the educated are facing each other on the question of what are the appropriate differentials for education, and the issue is sometimes quite hot.

It was not this issue, however, which forced a slowdown in the rate of educational expansion. It was simply lack of money. By the time that the number of children entering primary school approached 50 per cent of the age group, the strain on the budget was already terrific. Somewhere beyond 50 per cent government after government was forced almost to a halt, despite the fact that most of them have also increased their tax revenues very substantially over the past fifteen years.

People now began to look around for ways of reducing the cost of primary education. The idea of recruiting only highly trained teachers had long been abandoned; the primary schools were already loaded down with teachers who were only a step or two ahead of their pupils. Also abandoned were the dreams of the architects. In the middle 1950's the school architects in Africa were engaged in designing magnificent structures; the school was to be the centerpiece of the village and the pride of the whole community. The only snag with this conception is that architects' dreams cost the earth, as any of you who has built a house will know. By 1965 architects were under the strictest instructions to design the very simplest mass-producible structure for the towns; and in the countryside the villagers were being urged to build their own schools with voluntary labour and local clays, without benefit of architect.

But all this doesn't help much, since in primary schools the main item of cost is the teachers' salaries.

Next, people interested themselves in new techniques which might perhaps reduce the number of teachers per 1000 pupils. They studied the possibilities of radio, television, programmed learning, team teaching, and all the rest. But unfortunately the new techniques increase the quality of teaching rather than reduce its cost. Some require more teachers or better teachers to make them effective. The mechanisation of medicine has greatly increased its quality over the past thirty years, especially in the area of diagnosis, but it has increased rather than reduced the number of trained persons per thousand patients. In the same way we are still waiting in education for an effective innovation which will reduce the number of teachers per thousand pupils without also reducing the quality of the teaching.

However devoted one may be to an objective, as it becomes clearly unattainable, one inevitably begins to review how much priority it really deserves. The rejected suitor soon discovers that the girl is not really all that beautiful.

Just as the cost problem came to a head, the graduates of the new schools began to hit the labour market in increasing numbers, casting doubt whether it really was worth while spending all that money on primary education.

One must go back to the roots of the question. What is the purpose of a primary school? In the western world the answer is to help prepare the child for the adult world in which he is going to live. This simple answer does not fit the African village. The things with which the school concerns itself are not romotely like the world of the child's parents. However you look at it, an African primary school is a vehicle of modern ideas; not only does it teach reading and writing and counting, thus opening up a world which is completely closed to the child's parents; but also it inculcates an attitude of mind – the rational or scientific – which is at odds with the traditional and authoritarian aspects of his culture. If in the western world the school is an integrative force, in the African village it is a disruptive force, inevitably in tension with the society around it. The school definitely does not fit the child for the world of his parents; on the contrary it unfits him for it.

This tension is greatest in the countryside. African towns are a part of the western world, and urban African children need schooling to the same degree as urban children anywhere else. Indeed they need school rather more. In the western world the culture of the home and the culture of the society are much the same. If the child did not go to school, the kind of skills and ideas that he would naturally pick up from his parents would not be very different from the kinds that he would pick up at school. But African towns grow rapidly by immigration from the countryside, so the parents themselves are out of tune with the urban environment into which they have now moved. So the urban African school performs the same acculturation function as American schools performed for immigrant children. It gives then a new culture, different from that of their parents, but nevertheless what they are going to need to survive in their new environment.

Let us illustrate some of these differences. There is the language difference. In the village one speaks the tribal tongue, but in the town you can't make big progress without knowing English or French, as the case may be, and that you will learn in school. There is the tribal feeling. In the village you belong to a tribe whose traditional patterns of family obligation and political obligation dominate your life. These things fall away significantly in the town, where members of many different tribes live side by side; where the nuclear family is supplanting the obligations of the extended family; and where government is not by tribal elders but by the elected municipal council, on which may be sitting members of different tribes. Any school in any part of the world is engaged in acculturation as well as in teaching reading and writing and arithmetic, but there are few places where the acculturation function is more important than in an urban African school.

The school in the village is quite a different matter. In the village the parents and the society are in tune with each other. The society has elaborate and well thought out practices for educating its children, not in reading and writing, but in the habits of the adult world that they are about to join. A village school, run by trained teachers who have had at least twelve years' education, is bound to be a part of the modern world, while the African village is not. If one asks what is the purpose of the village school, one cannot answer that it is to help to prepare the child for the adult world in which he is going to live. Leaving unanswered the question of purpose, one is forced to note that its effect is to disrupt the community.

The evidence began to mount as children left the rural schools and made a beeline for the towns. The towns had no jobs for them, so they drifted into casual employment, unemployment and delinquency. The rapid growth of African slums is one of the more frightening features of recent years.

Wherever this situation occurs – and it has many precedents outside Africa – people have always been quick to blame the curricula of rural schools. The fault, they say, is that the schools are not in tune with rural life; and in particular that they do not have school gardens. The educational experts have always rejected this complaint, in my view rightly. In the first place school gardens are not all that easy to run, even when you have teachers trained to run them, which Africa has not. The garden has its own demands as to numbers and timing, which do not always fit the school year or the school curriculum. In the best educational systems the school closes at the height of the agricultural season, so that the children may help on their parents' farms; this eliminates both the possibility of and the need for a garden. In lesser systems, who is to look after the garden in the school vacations, and what is to happen to lessons in those parts of the agriculutural season when the garden demands full-time attention?

This is not, however, the heart of the matter. In fact, if the primary school could get good teachers of agriculture and devoted more time to farming it would become even more disruptive, since what it would teach the children about agriculture would be at variance not only with the practices but also with the attitudes of their parents. It would certainly not prepare them for cultivating three acres with a hoe, which is what their parents do. It would raise their horizons, both as to what they could do, and also as to appropriate reward for their labour, and they would come out needing instead to cultivate 30 acres with a tractor. The basic tension between the school and the community lies not in the subjects taught but in the fact that the school belongs to the modern world, and the rural community does not. It is thus inevitable that, as the modern school invades traditional rural communities, its more adventurous products will make a beeline for the towns.

This phenomenon is not new; it has occurred wherever schools have suddenly spread rapidly through the countryside, as in Europe in the last quarter of the nineteenth century. That period, you will remember, saw a vast migration from the European countryside to North America and the temperate parts of the southern hemisphere, reaching a peak of nearly a million persons a year just before the first world war. Schooling was not the only cause of this vast migration, which involved illiterates as well as literates. In any country where rapid economic change begins, the social equilibrium is disturbed. People begin to hear of wider opportunities outside their village, and they begin to move. The spread of schooling coincides with such changes, and reinforces them, but in Africa, no less than in Europe, it is not the only force making for a big tendency to migrate from the villages. And only in Africa is the movement led by the school leavers.

School leavers have played a bigger part in migration in Africa than elsewhere because of the peculiar structure of the school system. In Europe two centuries ago the number of secondary schools and universities was large relatively to the number of primary schools, so there was never a shortage of trained persons for middle and upper jobs. In Africa, as we have observed, secondary and university training were almost non-existent until fairly recently, so the primary school graduates occupied the middle jobs. Any youngster who completed primary school could expect a well paid white collar job. This set up expectations that could no longer be fulfilled when half the children were entering primary school. Through the fifties and early sixties the primary school leavers continued to expect such jobs, and to pile up in the towns looking for them. Gradually they adjusted to reality, somewhat bitterly. But in the interval these false expectations played some part in bringing to the towns more youngsters than the towns could support.

That was a temporary phenomenon. More lasting is the widening gap between rural and urban incomes in Africa. The farmers' incomes have been kept down deliberately in several countries, since the government buys their produce at one price and sells it at another. Through this and other devices, the bulk of the taxes falls on the farmers. At the same time trade unions have been raising wages continually in the towns, so that for example in Nigeria the minimum wage in Lagos for unskilled labour is now twice what is paid for unskilled labour in the countryside. Add to this the fact that the proceeds of the taxes levied in the countryside are spent mainly in the towns, providing water supplies, hospitals, electricity, secondary schools, and so on. One can only conclude that in these circumstances any intelligent young African who left school and stayed in the countryside ought to have his head examined.

The African economy differs from the European economy at the end of the nineteenth century in two respects which make the rural exodus more difficut to absorb. The first is that much of the European exodus was from one countryside to another. Agriculture was profitable in North America right up to the first world war. The period of the great European migrations is associated with the opening up of the Middle West by the railways, for a highly productive and rapidly mechanising agriculture. It is doubtful whether the system could have worked if American agriculture had not taken in so many people at that time. By contrast in Africa the movement is all into towns, and they cannot absorb the kinds of numbers who want to come.

The second difference is in the rate of population growth. The non-agricultural labour force of Africa is about 10 per cent of the population. Bearing in mind the cost of expansion, in terms of capital for houses, factories and so on, it cannot afford to grow faster than 4 to 5 per cent per annum. It must annually recruit another 4 or 5 per cent to replace those who die or retire, so its potential annual recruitment is about 9 per cent of itself, or, say, at most one per cent of the population. Owing to the high birth rate the numbers aged 15 and seeking work are between 2 and 3 per cent of the population. It is therefore absolutely impossible for non-agricultural occupations to absorb even as much as one half of the young people reaching age 15. The other half must definitely remain in agriculture. This was not so in Europe, since the non-agricultural population was larger in 1870 – about 50 per cent in Western Europe – and population was increasing more slowly – only by 1 per cent per annum instead of 2½ per cent per annum.

Now it is no tragedy that the non-agricultural occupations cannot absorb half the youngsters, because the other half are needed in agriculture. Africa is relatively underpopulated, so cultivable land is not a problem, as it is in India. Africa's growing population has to be fed, and its multiplying factories need raw materials. Food imports are already mounting sharply in some countries. It is all right economically to keep half the youngsters in agriculture; the problem is how in practice to get them to stay there. Or more particularly, in our context, how to get them to stay there and to have primary schooling at the same time.

These reflections on the effect of the primary school in the village, coupled with growing unemployment and the high cost of education all led to the same conclusion that primary education was expanding too rapidly, and should now be slowed. And this is what has happened. Over the past five years or so there is a notable slowing of enrolments, even though there are only three countries where as many as half the children are in school. Let us take a few examples, from the *U.N. Statistical Year Book*, which gives the figures for 1964. I shall assume arbitrarily that 20 per cent of the population should be in school; this is on the low side. On this basis Ghana stands out, claiming 90 per cent of its children enroled in school; closely followed by Gabon, claiming 80 per cent. Next comes Kenya with 55 per cent. The Ivory Coast and Malawi claim 45 per cent. Around one-third we find for Nigeria, Tanganyika, Uganda, Senegal; and under 10 per cent in some of the poorer countries such as Niger, Upper Volta and Ethiopia. The proportions entering school for the first time are of course much larger than these figures, because of the high dropout rates. One should note the wide range of variation among the 30 or so countries of Africa. This variation is found in almost every sphere. Any generalisation about African countries is likely to be false.

Clearly the problems I am talking about are not of equal magnitude in all these countries. Given proper levels of taxation the budgetary problem should not begin to be serious until the proportion of children in school passes 25 per cent. But of course many of these countries do not tax themselves adequately, so budgetary pressure may be felt at any level. The disruption problem begins as soon as the schools pass from the urban areas into the towns; i.e., as soon as the proportion of children begins to exceed 20 per cent. It is therefore now felt in all the more advanced African countries.

Necessity being the mother of invention, all those countries which are slowing down enrolment are finding good positive reasons for doing so, beyond the negative reasons of braking budgetary strain and social disruption. The most important of these reasons is the case for consolidation. Rapid expansion of schooling has meant a considerable deterioration of quality. Teachers are poorly trained. Wastage rates are enormous. Buildings, equipment and books are inadequate. Curricula need to be modified. The administrative system needs to be strengthened, so that school inspection and supervision can begin to be effective. When systems expand as rapidly as has been occurring one can be sure that a lot of money is being wasted. So an impeccable case can be made for calling a halt to ensure that one does properly what one is already doing, before taking on a bigger load.

The case is impeccable, but the disadvantages are equally obvious. One of the disadvantages is the effects of leaving the countryside without schools. It is not an argument against rural schools to say that they disrupt rural life, since the disruption of rural life is precisely what you want to achieve if you are interested in economic development. That this will cause a lot of rural children to head for the towns is unfortunate, but it is only a phase, since sooner or later the word gets back to the villages that there is nothing to do in the towns. The historians tell us that Western Europe achieved both its agricultural and industrial revolutions with only 50 per cent literacy. However the African countryside needs big technical and structural changes to increase its yields – to get 30 cwt. of maize to an acre instead of 7 cwt., as is now possible; to end the situation in which half the calves die within their first 18 months; or to substitute thirty acres with a tractor for three acres with a hoe. We can move some way to these changes through adult education, using those types of agricultural education which do not depend on literacy. Indeed we must rely heavily on adult education, or the situation will change only at snail's pace, as the young take over from the old. But it would help immensely to make all the young generation literate, and to use the schools to give it a more scientific attitude to life. Some social disruption is one of the costs of human progress.

It is also basically unfair to deprive the countryside of schools when the country people pay such a high proportion of the taxes. It is not entirely a caricature to say that most of the new African states are societies where a few educated people are milking the farmers to provide for themselves nice jobs in nice towns. The farmers have put up with this because it is difficult to do otherwise in authoritarian regimes, but there is no doubt as to their dissatisfaction. They are undoubtedly entitled to a larger share of what they produce than they are getting now.

How then is one to break out of the present box built by shortage of money and reactions to the rural exodus?

One of the possibilities is a major change in the primary programme, cutting the schooling offered to four years. The British and French African countries all started much more ambitiously than this. The British elementary system, for instance, provided about ten grades, though it was assumed that most of the children would not stay for more than 7 or 8 years, and indeed in Africa most do not even stay for five. The argument now is that if you cannot afford to give eight years to more than half the children, it is better to give four years to all the children. This argument, incidentally, was the basis of primary education in the Soviet Union. The educational case is that if half the children will have left school in four years anyway, it is better to start them in a programme designed for four years, than in a programme designed for eight years. This argument may in practice turn out to be an illusion. It has been remarked that it is always difficult to get a school to design its programme on the assumption that most of its pupils will go no further educationally, as is usually the case. In practice, as distinct from theory, the purpose of schools is to provide raw material for further schooling. Primary schools prepare their children for secondary schools; secondary schools prepare for colleges; colleges prepare for graduate schools; and graduate schools prepare people to be professors. Anybody who enters the primary school at one end and does not come out at the other end as a professor is a drop out from the educational system. Nevertheless, with hope triumphing as usual over experience, one may hope that it would be possible to design a four-year curriculum specially suitable for the rural African school.

One could not easily introduce a four-year system into schools which are already on an eight-year basis, since this would produce a big political fight with parents. But it can be done in areas which do not yet have a school, especially if accompanied by the assurance that good students who complete the four years will have a chance to go further in another school – for it is not only the teachers but also many parents who believe that the purpose of one school is to prepare you to go on to another.

This particular change would reduce costs somewhat, but not by all that much, since the drop-out rate is already so high anyway. The cost is the same whether you have an eight-year system, half of whose students have dropped out in the first four years, or a four-year system half of whose students go on for a longer period. The main advantage of the four-year system is presumably that it can be better designed for its purposes, and thus may give better value for the money. But how much it would actually reduce costs depends in each country on how big the drop-out rates are in the existing system.

Since high cost is inevitable, and budgets are strained, the next possibility is greater foreign aid. Africa receives very little foreign aid from the United States – less than 200 million dollars a year directly, plus the American share of what goes through the United Nations and the World Bank. In any case, there is intellectual resistance to the idea of using foreign aid to pay teachers' salaries, which are as much as 80 per cent of the cost of primary schools. Donors feel that their aid should pay for goods that they export, such as machines, or for the services of their nationals who go overseas to work. The French, who give very substantial aid to their colonies in Africa, do maintain a large corps of French teachers there, especially in the secondary schools and universities. The United States has Peace Corps teachers in Africa, and the British maintain teachers there under their similar schemes. But this does not much affect primary education directly; which would be enormously expensive if one had to pay Franch or British or American teachers, instead of using African teachers at $500 a year. What primary education needs is not foreign teachers, but foreign money to pay African teachers, and this is not forthcoming.

Of course the money does not have to be tied directly to primary education. Anything that relieves the budget makes it possible to spend more money on primary education. For example, the British could say "if you will spend more on primary education we will pay the salaries of all British teachers in the university". Any increase in foreign aid to one sector of the economy releases funds that can be used in other sectors. The main difficulty therefore is not that primary education as such is not aided, but rather that foreign aid as such is now in the doldrums. After rising rapidly in the fifties and early sixties, it has now been stationary for some years, and American aid is actually falling. This is due to several causes. One cause is the erroneous idea that foreign aid has not done any good. One reads such nonsense as that the poor countries are getting poorer while the rich get richer. If this were so, foreign aid would indeed be money down the drain. But it is not so. Over the past fifteen years, the national incomes of poor countries have been growing as fast as the national income of the rich countries, at an average rate of 4½ per cent per annum, and some of the fastest growing countries in the world have been in Africa, notably the Ivory Coast and Nigeria. The per capita rate of growth, allowing for rising populations, is as high as anything the United States has achieved in its history, namely, 2 per cent per annum, and higher than anything achieved in England since 1870. In other words, the story of the underdeveloped countries over the past 15 years is a success story, and foreign aid has contributed to that success. This is no time to grow weary of well doing.

Let me return to the African scene. The upshot of all that I have said is that the pace of expansion of primary education has to be adjusted to what the community can bear. We must not assume that the community can bear only what it is bearing now. On the tax side, some of these countries with less than 20 per cent of children in school could be doing much more to help themselves. African countries vary enormously in the proportions of national income paid in taxes, and in the degree of effort made over the last 15 years. Neither should we take it for granted, in considering the descriptive effects of rural schools, that the school must adapt its outlook to an agriculture of three acres and a hoe. On the contrary, if the school does not fit the agrarian structure it is because that structure is due for change; every African government needs urgently to have agricultural policies which will make it possible for the young school leaver to enter a new agricultural system which offers him a reasonable future, both in terms of income, and in terms of the intellectual and other challenges that it presents. To be realistic, however, we must recognize that agriculture changes relatively slowly, and that if the schooling goes far ahead in pace, school leavers are bound to be frustrated. In the Western world we take it for granted that more and better schools are the chief solution for most social problems; it may have interested you to have this picture of communities where schools sometimes create more problems than they solve.

HEALTH PERSPECTIVES

Hon. Wilbur J. Cohen

Former Secretary of Health, Education and Welfare;
Professor of Public Welfare Administration,
University of Michigan, Ann Arbor, Michigan

In 1893, the noted historian Frederick Jackson Turner, described the conquest of the physical frontier which had dominated American thought and actions for over a century. Today, I believe we are confronted with a vast social frontier which challenges us to remove the barriers of human want, ignorance and illness.

We have made headway in recent years in the conquest of this frontier. The Executive branch of the Federal Government, the Congress, the States, and the Public have acted to attack some of the ancient enemies of mankind – hunger, disease and human blight. As I look back over the past eight years I see some significant milestones of progress.

- In 1960, there were 40 million persons in poverty. Today there are 18 million less than in 1960.
- In 1960, there was no coordinated attack on poverty. Today the poor now have a better chance to find decent jobs, homes, health care, and education for their children.
- In 1960, in some schools, as many as 60 percent of the students enrolled in the 10th grade dropped out before graduation. Over the past 8 years the high school dropout rate has been reduced by 10 percentage points.
- Eight years ago millions of Americans over age 65 were without adequate health care because they could not afford it. Today 20 million older Americans are protected by Medicare.
- In the past 8 years Congress has enacted over 50 new health laws designed to assure the right of every American to high quality health care.
- In the last 18 years – the life of a teenager – we increased the proportion of our Gross National Product spent on health, education, welfare, and social security – private and public – from just over 12 percent to almost 20 percent. This year we will invest over $55 billion on health services, research, and construction.

In human terms, these new laws, programs and increased expenditures have helped to bring about significant improvements in the health of the American people:

- Infant mortality is at the lowest rate in United States history.
- The lives of thousands of children have been saved that would have been lost to diseases in early infancy and childhood.
- The death rate from heart disease has been reduced 20 percent in the past 4 years.
- Dramatic declines have been recorded in the number of resident mental hospital patients.

These dramatic improvements are a result of the increased investment that the people are making in one of their most important resources: good health.

"The first wealth," Emerson once said, "is health." However, the most affluent

Nation on earth still cannot claim to be the healthiest one. For there are still too many obstacles, some of long standing and some recent, that bar many citizens from receiving even barely adequate health care.

The American health care system is essentially a mosaic of public and private health programs – one that has grown piecemeal to meet needs as they arose. There are a multitude of people, institutions and arrangements involved in the system. There are a total of over 3 million health workers, including 300,000 physicians in a variety of practices and 700,000 nurses. There are 7,000 hospitals varying greatly in size and in operation, some 20,000 long term care facilities; there are local and national voluntary health agencies, and professional groups; medical schools; hundreds of insurance companies, local, State and Federal agencies; consumer groups; and a variety of payment mechanisms, including fee for service, prepayment and charity, which further complicate the system.

This dynamic, pluralistic system has significant advantages. It provides opportunities for innovation and competition for quality development, and incentives for organizational and quality improvements. And the system has produced amazing medical miracles.

But out of this system has evolved a number of serious problems which are likely to continue to face us in the decade ahead. Among the most serious, I would include the following:

1. The supply of certain services, such as those of physicians, dentists and nurses, is inadequate.
2. There is often an excess in supply – duplication – of some services and facilities for high income individuals, including some very expensive hospital services; and health facility planning is not now performed adequately.
3. Children, the poor, the disadvantaged, and the blacks, often have inadequate access to medical care.
4. There are often shortages in less costly alternatives to hospital care such as outpatient care, home health services, extended care facilities, and nursing homes.
5. Some costly services, especially hospital services, sometimes are utilized unnecessarily.
6. Many private health insurance plans produce undesirable incentives to use the most expensive methods of care.
7. There are substantial gaps in the coverage of health insurance.
8. The costs of drugs is too high.
9. Many possible hospital management improvements have not been adopted.
10. The growth of group practice has been retarded by legal bars and restrictive attitudes.
11. Productivity in the provision of medical care has not been defined and measured.

12. Insufficient attention is given to preventive care and health education.
13. There are insufficient financial incentives to restrain mounting hospital costs while maintaining high quality medical care.
14. Ignorance of quality comparisons or the failure to undertake them have resulted in the purchase of high priced drugs or unnecessary services.
15. There has been unsatisfactory organization of activities at all levels. – public and private – in the health field.
16. There are serious deficiencies in the organization, financing, and delivery of health care in the United States.

These problems create obstacles to the provision of adequate health services for all Americans. Although the poor suffer most from the inadequacies of the system, American families of all income levels are experiencing the consequences of our piecemeal system.

We face certain scandalous realities – for example, an enormously high infant mortality rate. While this is far more than a medical matter, it is only through extension of health measures in the broadest sense that one can hope for a solution. The point is driven home in vivid contrasts – in the terrible wastage one sees within cities that can boast, for their more favored residents, of very low rates by any standard. In New York City, for example – where the overall infant mortality compares with the national average of about 24 – there are neighborhoods where the rate is as high as 47 and others where it approaches 12. The difference of 35 annual deaths per 1000 infants under 1 year of age must be considered excessive.

Indeed, there are a dozen or more nations in which a newborn child has a better chance of surviving than he does in the United States. We must have a comprehensive Child Health Act in the United States which will provide complete and adequate health services to every child.

What are we going to do to remove the financial, the physical and psychological barriers to health care?

I do not have any simple solutions for these complex problems. But I would like to discuss a few aspects of the problem of health care costs and to give an idea of some approaches that may be worthy of further investigation and effort.

Aside from the scientific and technological marvels in the field of health, the greatest health care accomplishment of recent decades has been the discovery and use of health insurance.

During the past two decades the extension of private health insurance protection to the working population and their families has been impressive. At the end of last year between 75 to 85 percent of the population under 65 had some coverage of hospital and surgical expense. But despite this impressive coverage, health insurance benefits in 1967 met only about 33 percent of all consumer expenditures for health services.

Advances in the medical sciences have tremendously increased the ability of modern medicine to cure or relieve disease. But the costs of care have multiplied, and can be prohibitive for everyone. People with low incomes need the protection of health insurance more than those with high income. Yet the extent of health insurance coverage varies in reverse degree. In 1967 only 35 percent of persons under age 65 with family incomes under $3,000 had some hospital insurance and 57 percent of those with incomes between $3,000 and $5,000, as compared with 90 percent among those with incomes of $10,000 or more.

The expansion of health insurance to its present dimensions testifies to the need for and the popularity of insurance protection against health care costs. Nevertheless, private insurance still falls seriously short of the mark. Some 15 to 25 percent of the population under age 65 have no health insurance protection. Among these are millions of otherwise self-supporting people who must rely upon public or private help when serious illness strikes or go without care.

The disabled, too, are greatly in need of health insurance protection. Yet in 1966, half of the severely disabled aged 18-64 had no protection.

Millions have protection that is quite meager – covering only part of the cost of needed services for a limited duration of illness. They can be overwhelmed by castastrophic medical costs.

Moreover, health insurance emphasizes protection against care and medical services in the hospital. In fact in the great majority of cases – where there is any protection against out-of-hospital health care expenses it is so seriously limited that only a small part of the expenses are reimbursed. By encouraging hospitalization rather than appropriate alternative types of care private health insurance has a major effect on health costs. Private insurers must find ways of increasing the proportion of health and medical expenditures that is met through voluntary insurance. The need and the opportunities are present. Improvements in private health insurance protection would limit the need for expanding Medicaid. Higher levels of employment and income should provide more opportunities for people to take advantage of voluntary health insurance.

Private insurers, employers and unions will have to find ways to finance more adequate coverage for workers in large industrial firms. But ways must also be found to make such coverage available to employees of very small businesses, to farm employees and farm managers, to private household workers, and to those who are currently unemployed. Unless these people are protected a serious vacuum will develop. These gaps give rise to the demand for public programs.

In addition to improving protection for workers whose employers share in the cost of insurance, private insurance will need to support public financing measures which are needed for those who are too poor to afford health insurance premiums or whose employers do not share in the cost. One way to assist in this effort is for private insurers to support extension of Medicare to the permanently disabled under 65. I also believe that Medicare should be extended to cover the costs of some of the essential and continuing prescription drugs needed by the aged and the disabled.

The Secretary's Advisory Committee on Hospital Effectiveness, chaired by Mr. John A. Barr, Dean of the Graduate School of Business at Northwestern University, has pointed out that some of the most serious problems have their roots in obsolete financing methods which serve as barriers to health care. The committee recommended legislation that would authorize future Federal financing for health facilities and services only in States which set standards for health prepayment and insurance policies, and limit the cancellation of policies.

Another recommendation calls for a Federal or State requirement of a minimum range of benefits for health insurance including not just hospital inpatient services, but outpatient ambulatory services, extended care services, home care programs, and physicians' services in and out of hospitals.

These are excellent suggestions. I urge that you study the Barr Report carefully. The relative roles of private insurance, social insurance, and other publicly-sponsored and financed health benefits are still matters of study and lively debate. I believe, however, that private and public insurance can play a much larger role and result in the coverage of every person in the United States for comprehensive, high-quality medical care.

But what of the role of government? For one thing, government is needed to provide protection for high risk groups such as the aged and the disabled. Through various combinations of public and private efforts the Federal Government must help to finance additional health care for mothers and children, for people in the ghettoes, for migrant workers and for others whose incomes are so low or whose employment is so marginal that they are not being reached.

Both public and private insurance must respond to the great need that still remains. Public programs should not be viewed as competitive. They are not destructive of voluntarism. Indeed they can be supportive.

All of us in the health field must strive for new arrangements. Solutions in the medical field are not simple. We should preserve the mosaic of public and private health services financed through public and private resources. We must work closely with leaders in the voluntary health insurance field to find ways to expand and improve voluntary insurance coverage. We must also enlist the aid of consumers, the poor, and professional people.

Coverage of expanded services will cost more money. As the ones who pay the bills the government and the private sector must work together to find methods to promote efficiency and economy. Through third party reimbursement formulas, improvements can be encouraged and supported. High priority must be given to implementing the provision of the 1967 Social Security Amendments that provide for experiments with methods of reimbursement that contain both incentives for economy and safeguards for quality.

During my service as Secretary of Health, Education and Welfare, I approved the first four experiments. Two are designed to test the effectiveness of specific reimbursement formulas. One seeks to restrain costs through cost comparison and consultation to improve management practices. Another would test a per capita rate covering all medical, home care, and institutional services and would be added to the program of a group practice plan now reimbursed for only non-hospital services. I hope that more of these experiments will be approved in the near future. This program offers the health care field, including the insurers, a tremendous opportunity to try out new ideas.

The improvement of health insurance is one of the most important steps that can be taken to break down the financial barrier to health care.

But other measures are also vital. We need more and better nursing homes, extended care facilities, home health services, community mental health centers, and neighborhood health centers. But we must also plan intelligently for these expanded facilities and services. We must have effective community and statewide planning. If unnecessary facilities are built they should not be a basis for increased charges under any health insurance or medicaid program.

We need more doctors, nurses, technicians, and other health workers. Other countries are producing more than the United States. Russia, for example, with a population of 250 million graduated 35,000 doctors last year, whereas we, with a population of 200 million graduated only 8,000. I say we can do better. I believe that every boy or girl who qualifies for medical school should have the opportunity to enter medical school. This would involve a doubling of the entrants into medical schools. I believe we should make this our objective during the next decade.

We also need much more preventive care. Think what we could do to prevent disability, lengthen lifespan, and at the same time moderate health costs? Because of this I appointed a distinguished group of men and women before I involuntarily left as Secretary to study and recommend preventive measures. Dr. Arthur Flemming, President of McAlester College, is Chairman of this Committee and I look forward to the recommendations of the group.

To do all these things we must plan much more systematically and comprehensively. We must develop and test new ways of delivering health services. We must have a health system that works for all of the people, all of the time.

To make it work we need public discussion, debate and involvement. The dialogue has begun, particularly since the enactment of Medicare.

The Federal Government must take the leadership to continue the dialogue in new settings and with new people. It must be particularly concerned that consumers participate in the development of health policy. It must be committed to strengthening every partner in this whole health team.

Some of the questions which I believe should be discussed in the new dialogue are:

1. Federal and State financing of part of the cost of emergency hospital services, outpatient and home health services in order to reduce the use of more expensive inpatient hospital care;
2. Subsidy of part of the salaries of interns and residents so that the educa-

tional aspect of these services would be born by the general community and not as a part of a hospital patient's bill;

3. Special payments over a two to five year period to hospitals and nursing homes where they undertake significant incentive programs;
4. Incentives to hospitals and other institutions to take advantage of combined services for laundry, food handling and purchasing;
5. A special study of the costs of malpractice insurance with a view to lowering its cost;
6. Adding non-professionals to licensing boards for professional health personnel in order to stimulate greater public awareness of and interest in the health manpower shortages;
7. The removal of State impediments to group practice, the establishment of State group practice advisory boards, and the provision of adequate financial bases for beginning groups.

Today we are on the threshold of an exciting new era in health care. I am confident that we will move into the next decade and beyond on a wave of medical progress that will make achievements to date seem almost commonplace by comparison. Yet such progress will not occur without the full participation of the medical profession, the Government, and the American people in taking up the great unfinished tasks.

I believe that we can assure every American the right to good health care. And I intend to do every thing within my power to fulfill that right.

I ask your help and dedication in this great effort.

SOME THOUGHTS ON PEDIATRICS OF TOMORROW

Sidney Farber, MD.

Chairman of the Staff of the Children's Hospital;
Director of Research of the Children's Cancer
Research Foundation; S. Burt Wolbach Professor
of Pathology, Harvard Medical School.

It is my privilege to speak on this historic occasion for the staff and for the large number of devoted men and women who comprise our Hospital family. This gathering marks the celebration of a century of survival of an institution, and far more important, the realization of the plans and dreams of large numbers of people: devoted trustees and administrators, dedicated doctors, and nurses, and paramedical workers, and a deeply interested public. Throughout our history we have been blessed with the support of devoted trustees who have faced with courage the constantly increasing needs made evident by the great advances in the care of sick children. The staff acknowledges the courage of the present Board, under President William W. Wolbach, and his administrative staff under Dr. Leonard W. Cronkhite, Jr., for proceeding with the implementation of plans derived from studies of the last thirty-five years. We speak of our pride in our splendid nursing training school, and in the devotion of a large army of people in all kinds of paramedical and supportive activities who comprise the Hospital family. The long years of devoted service of the Women's Committee mark an achievement of enormous value to the welfare of our patients, and finally I should like to state, with as much objectivity as possible and with no embarrassment, our great pride in the quality of our staff manifested by achievements which are recognized the world over. The conservative statement may be made that with the new facilities for the care of patients and the large and first rate provisions for laboratory investigation in our new research building under construction, the contribution of the staff in behalf of sick children will be enormously increased in quantity, in quality, and in overall effectiveness.

With these happy words, may we turn now to our beginnings when Dr. Francis Henry Brown and his colleagues and high-minded lay supporters a century ago believed that there was overwhelming need for an institution devoted to the care of the young. Their vision was great enough to include not only the main goal of medical and surgical treatment of diseases of children, but also the attainment and diffusion of knowledge and the training of young women in the duties of nurses. They had in mind also the acquisition of specialized knowledge of pediatrics, the better to teach medical students and train doctors.

In their first appeal in 1869 for support in behalf of a hospital for children they stressed, in addition to these goals, the needs of the poor, or what we call today, the disadvantaged. Their description of the lot of children of what they called the poor classes, made a compelling case for their proposal. They concluded their statement with these words: "We desire to afford these sufferers, for darkness, the sunshine from heaven; for filth and disorder, cleanliness and system; for the rough word or neglect, – may chance a blow or threat, – gentleness, kindly attention, encouragement; for mephitic odors, sweetness and purity in their truest sense."

In these remarks we shall make reference to one children's hospital, but we will do this with full acknowledgement of the great debt we here owe to the institutions and medical workers throughout the world whose own great progress inspired and helped to make possible what has been done here. We salute in particular those institutions whose representatives are here today to join with us not only in this celebration, but in proper acknowledgement to all who have worked in behalf of children during the past century. We are grateful to those who have travelled from other countries and many parts of the United States to celebrate with us, and mention particularly our indebtedness to the children's hospitals in Europe, including the Hospital for Sick Children at Great Ormond Street where Dr. Brown received inspiration. We recognize the presence here today of representatives of the first Children's Hospital in this country, situated in Philadelphia, and finally we express our gratitude to the largest organization in this country devoted to pediatrics, the American Academy, which under President Dr. Hugh C. Thompson has welcomed our Centennial Celebration as a prelude to their own important meetings.

Through the remainder of the 19th Century, and the first third of the 20th, progress in pediatrics in many institutions was made through the contributions of clinicians in the several specialties concerned with the child. In 1939 at the celebration of the 70th Anniversary of the founding of our Hospital, acknowledgement was made of the fact that our hospital could be called a true *general hospital for children.* On that occasion we stated "the last fifteen years have seen tremendous strides in the effectiveness and organization of all departments of the Hospital. Each has progressed to an important degree. And yet not antagonistic to the development of each individual department has been a remarkable and happy integration of activities of all services and divisions bringing together in an attack on the problem of disease in early life techniques and types of knowledge of a variety and magnitude not to be found on any one clinical service. This integration has strengthened rather than weakened each of the divisions of the hospital, and has served to break down artificial boundaries between clinical services and to prevent the dangerous products of specialization."

When the second World War ended and attention could be paid once more to advancing the health of children and of all people, the time was ripe for the creation of a Medical Center for Children. The nucleus of this Center was the Children's Hospital and the Infant's Hospital. The essence of the Center was the bringing together of all the specialties in medicine, surgery and laboratory science for the solution of problems of the infant, the child, and the adolescent. The heart of the Center was the interdisciplinary attack in the care of our patients and in research and education, crossing all departments and converging in the achievement of a plan for *total care* of the *child* for the first time, on this scale, in our history.

The plans for the expansion of the Children's Hospital into the Children's Medical Center, twenty-three years ago, can be described also in terms of the creation of a regional medical center for infants, children and adolescents. It is this conception which is under trial at the present time in the fields of heart disease, cancer and stroke. This preceded recent activity in the creation of substations of medical centers in the communities where doctors are lacking and the unmet needs for medical care are enormous. It is this conception, too, which will enable community hospitals to increase greatly the value of their work with children, as in all other fields of medicine. The proper use of modern technology can bring the facilities of children's medical centers, and all other kinds of centers to the community hospitals for continuing education in the many specialties of medicine and surgery of importance to pediatrics, as well as diagnostic assistance and therapeutic advice. In the many fields of pediatrics, too, vital assistance can be given the doctor in practice by the availability in the Center, of an Information Service which ideally should be of two kinds. The first should be the compilation of all information from the literature, up to the moment, evaluated by experts, with infomation recorded on computers for easy utilization by any interested doctor. The second kind of information service is perhaps far more important, particularly for the patient for whom no recorded method of treatment is of value. This consists in the recording, with the cooperation of scientists and doctors throughout the world, of promising results of ongoing research which may be one or two years away from medical journal publication, or announcement at a medical meeting. There, of course, must be proper precautions to protect the priority of the investigator. Here, evaluation, again by experts, must be given of such research progress, with the information itself. Data made available to doctors through such centers will be of life saving value at a given moment. Such information services should be connected with all other similar centers through the National Institutes of Health, and perhaps appropriate voluntary health agencies or medical associations, not only in this country, but throughout the world.

We are working actively on such a plan in the field of cancer and urge strongly that such a resource be created without delay, with the cooperation of everyone concerned with the young.

Is research progress being made as rapidly as possible? We have no patience with pronouncements that within a year this, or that great discovery or breakthrough will be made, as, for example, a vaccine or cure for all forms of cancer. There must be no surrender by scientists or doctors to the temptation of flirtation with a fickle calendar. There should be no hesitation, however, in stating that far greater progress in the conquest of disease as a whole and in the field of pediatrics in particular, could have been made in the last 25 years alone had greater resources in facilities, support and manpower been available. The knowledge which made possible many of the great strides in infectious disease, could have brought answers to some of our pressing problems of infectious disease much earlier, because fundamental knowledge was already available. Let us take the example of German measles – rubella. This ordinarily mild disorder becomes a great importance particularly when a pregnant mother without immunity becomes infected in the first trimester of pregnancy. The several thousand unfortunate children who have disturbances to their eyes, ears, hearts, or brains, with sequellae of mental retardation or cerebral palsy, following the last great epidemic of German measles in this country, just a few years ago, will go through life with misery to themselves and to their families because a vaccine was not available at that time. There soon will be a vaccine, hopefully in time before the next great epidemic. There were not enough virologists with adequate facilities and support to approach this problem as one of top priority, overwhelmed, as virologists are, by many problems of infectious disease. When this problem was tackled because of inspiration of several different kinds, by several different groups, it was not long before the virus was isolated and not long after before an adequate vaccine was prepared. There are other problems in pediatrics which may not yield to highly competent research in so rapid a manner, and still others that may take decades to solve.

It should be emphasized, however, that present knowledge should permit much more rapid progress in many fields of pediatrics if we could but train more scientists from the pool of brainpower presently available, and keep our trained scientists in research by the availability of adequate funds for the support of research. I should like to convey to you a sense of enormous impatience based upon knowledge of what *could* be done, as compared with what *can* be done today because of the inadequacy of research support in all countries.

The golden age of medical research in this country came about since World War II because intelligent men of compassion in the Congress became better informed of the health needs of the country, through governmental health leaders, and a small number of citizen medical men and scientists who worked with a larger number of lay people dedicated to this task. Much of this progress came from voluntary health agencies which came into being because of the enormity of the unmet needs of our people. It was painfully apparent in 1948, to take one example, that the small number of doctors in childrens and general hospitals who became expert in improving the lot of the patient with cerebral palsy, were so overwhelmed by their clinical responsibilities and appalled by the meager support available for their work, that they could not meet the needs of parents of palsied children. When the parents *no longer* could face the enormity of their problems in the care of their crippled children, without the kind of hope that can come only from adequate care and facilities and the promise of research, they formed their own organization. This we have seen in the case of poliomyelitis, muscular dystrophy, cystic fibrosis, kidney disease, cancer, heart disease, and a number of similar problems. Such voluntary health agencies raised money which made possible better care and more research. This was of inestimable importance because it was a private attempt to do something about problems which affected their own children. More important in practical results was the education and inspiration of the Congress that came from the entreaties of these people and also of lay leaders who had no personal problem but believed that far more rapid progress should be made. The result of many such efforts, was the greatest backing ever given in the history of medicine for the support of scientists and doctors, as well as of their research and of research facilities and equipment. Small wonder the statement is made so frequently that "there has been more progress in biomedical science since World War II than in all prior history". Of course, people, and not money, do research, but without adequate funds there can be only slow progress. We face at this time a crisis in medical research, including all activities in pediatric research, because of the inability or failure of the Congress to appropriate adequate funds even for the maintenance of the level which has been achieved. This is a bitter situation and one which must not be permitted to continue its downward course. We face this deficit in research support at a time when there are tremendous needs which must be met in areas of great concern in the cities, including the problems of poverty. There need be no choice between these two. A country with a gross national product of such immense size should and must be able to afford both, without regard to other priorities, the importance of which are being debated throughout the land.

Pediatric progress has been aided greatly by the association of many children's hospitals with medical schools and universities. We are proud of, and grateful for our association with Harvard Medical School and the great University to which it belongs, and we have profited immensely from this association. In turn we have contributed to the medical school and the university great strength in teaching and in other associations. In all such relationships between pediatric activities and medical schools it must not be forgotten that the hospitals have needs unique to them and not necessarily shared by a purely educational institution.

What of progress in the decades ahead to 2069?

We may expect the conquest of more and more infectious diseases, until control of all infections, as we know them, will be achieved by vaccines, antibiotics, antimicrobial agents, and various methods of immunization. We may look forward to the control and prevention of the many diseases we call cancer by chemical and immunological means, and to the control, cure or prevention of other "dread diseases", to mention only a few examples, by:

1. greater biochemical understanding of inborn errors of metabolism
2. of genetically determined disturbances by genetic engineering
3. the intrauterine diagnosis and correction of abnormalities and diseases
4. the control of nutritional problems
5. the eradication of malnutrition
6. the correction and eventually the prevention of the many forms of congenital abnormalities.

It seems clear that new man-made disorders will arise and will have to be controlled, as industry introduces into the air we breathe, the food we eat, and our environment as a whole, new substances some of which may be toxic and productive of serious disease. We may expect that new man-made diseases may occur through the use of medicines as, for example, thalidomide. Such iatrogenic accidents must be recognized early, and large scale disease or death prevented. In the decades ahead, those diseases which are the chief causes of death today will be controlled, prevented or eradicated and the duties of the doctors in children's hospitals will be directed much more to the maintenance of the normal in mind and body, to the consequences of accidents, and to the problems of space medicine.

The great problems in psychiatry against which so much effort has been applied in the last 25 years will demand then far more attention. The present methods of treatment given by superbly trained and highly skilled professional workers in psychiatry, child guidance, psychology and related disciplines will be aided and finally supplanted by the definition of, and then the biochemical correction of the molecular or biochemical basis of misbehaviour, mental disease, and emotional stability. This is a terrifying assignment for psychiatry; but it can be accomplished with the help of the psychiatrists and scientists who are expert in the fundamental sciences of molecular biology, biochemistry, immunology and chemotherapy. When this happy day comes, many of our world problems and those in our immediate vicinity may disappear. It has been feared by some that the world *then* may be less interesting, but, if so, there will be the opportunity for relocation on other planets. Under such control of disease of the body and the mind, the Children's Hospital here, and all children's hospitals will continue in their transition from children's medical centers to Centers of Child Health, carrying over a tradition of expert, loving care by superb nurses and other medical workers, and by highly skilled doctors who choose to devote their lives to the well being of infants, children and adolescents. Their devotion to human beings of an age period will bring to them the greatest reward that man can receive today, and that is the awareness of what they are accomplishing in behalf of children.

Let us close on words of hope and conviction that there *will* be a celebration at the end of the second century of the Children's Hospital, and the Medical Center into which it has evolved; that the great Child Health Center which will have been developed during the second century will be closely involved with those concerned with the field of education; that the means of communication in 2069 will be so sophisticated as to link all health centers and all countries to make available the knowledge and strengths to all; that the problems of malnutrition will be a matter of history and no longer of concern; – that family planning will have resulted in a population the world can support, composed of human beings who nutritionally, physically and mentally will be able to produce children who will have the best chances for good life than can be conceived or produced; – that those who celebrate at the end of the second century will be able to record a true brotherhood of man.

Such goals are worthy of the greatest effort of all who love children and who want to insure for them fine happy and productive lives.

VACCINES FOR VIRAL DISEASES

OF CHILDREN –

PAST, PRESENT, AND FUTURE

Wendell M. Stanley, Ph.D.

Professor of Molecular Biology;
Director, Virus Laboratory,
University of California at Berkeley, Berkeley, California;
Nobel Laureate, 1946.

It is indeed a great honor to participate in the celebration by The Children's Hospital Medical Center of the founding of its first component, The Children's Hospital of Boston, 100 years ago. Although I am not familiar with the clinical activities of the Medical Center, I have followed with intense interest the great research accomplishments which have come from the Division of Laboratories and Research, including especially the component known as The Children's Cancer Research Foundation, since the establishment of these units in 1946. As a matter of fact, some years ago I spent a very brief period, one or two days I think it was, as Director-*pro tempore* of The Children's Cancer Research Foundation. This served to provide me with an insight to the work of the Foundation. The research accomplishments which have come from this Foundation are of the greatest importance in connection with the subject of this lecture – Vaccines for Viral Diseases of Children – Past, Present, and Future.

The first viral vaccine and one of importance to children was the vaccine against smallpox developed and used by Jenner about 170 years ago. Jenner's work was of great importance, not only because of the degree of protection the vaccine afforded against smallpox but more especially because it presented for the first time the idea of vaccination. Jenner first used his vaccine on his 18-month old son and later on an 8-year old boy. This vaccine has been gradually improved over the years and at present is produced on calf skin or in chick embryos. It is a live vaccine and its infectiousness is best preserved by drying. The use of this vaccine has reduced the incidence of the disease throughout the world and has eliminated it in several countries. Cases reported to the World Health Organization in 1967 totaled about 120,000 and in 1968 the number was reduced to about 60,000. For several years the only cases in Europe or the United States came from the introduction of the disease by individuals from endemic areas. The reduction in the incidence of smallpox in the United States since 1921 is most dramatic. It is obvious that so long as endemic areas exist in the world and man continues his extensive travels it will be necessary to continue to use smallpox vaccine in the United States. However, the fact that occasionally clinical complications follow vaccination is sufficient reason to continue efforts to improve the vaccine so that the already very low incidence of such complications following vaccination can be reduced still further or perhaps eliminated entirely.

It is surprising, in a way, that 85 years passed before another viral vaccine was developed and used. But this is the fact, for 85 years later or looking at it another way, 85 years ago, Pasteur developed and used a very crude vaccine against rabies. Here again the vaccine was first used on a 9-year old child and shortly thereafter on a 15-year old boy, both of whom had been severely bitten by rabid dogs and both of whom survived. The original vaccine was made from the spinal cords of rabbits inoculated with a fixed strain of rabies virus obtained after 100 passages in rabbits. The cords were dried at room temperature for different periods of time and emulsions of the tissue ranging from preparations showing no infectivity to preparations showing full activity were used in a serial manner over a period of several days. Pasteur thus introduced two important concepts, namely the modification of the pathogenicity of a virus for its natural host by serial passage in another host, in this case intracerebral passage of canine virus in a rabbit and the use of graded doses of a viral antigen. Despite the possibility of the induction of allergic encephalomyelitis from the use of a crude vaccine containing much brain tissue, the Pasteur treatment, as this type of vaccination against rabies came to be known, was widely used for many years mainly because the disease was regarded as being fatal for man. In 1938 rabies virus was grown in the chick-embryo and by passage in this host a strain was obtained with greatly reduced ability to grow in nervous tissue. A live egg-passage vaccine is now extensively used in dogs but has seen only experimental use in man. I anticipate that an egg or tissue culture passage vaccine with or without hyperimmune serum will eventually replace the killed virus rabbit brain vaccine still widely used in man.

Despite 85 years of development there is still room for improvement of rabies vaccine and because of modern techniques and knowledge an effective, completely safe rabies vaccine should become available in the near future. Since for several years we have had only one or two cases in man annually in the United States, a rabies vaccine may appear to be relatively unimportant. However, this is far from true not only because the rabies death is so horrible but especially because of the large number of people suffering bites from animals where it is not known whether or not the animal was rabid, hence causing great anxiety and mental distress. Furthermore, in 1964 there was a marked increase in the reported numbers of rabid wild animals despite the continuation of the decrease in the incidence of rabies in domestic animals where the use of the vaccine is being increased.

The development of the smallpox and rabies vaccines represents a great tribute to the ingenuity of Jenner and Pasteur for in those days the true nature of viruses not only was not known but viruses had not yet been recognized as a new type of infectious agent. This came about 15 years after Pasteur's work and the nucleoprotein nature of viruses was not discovered until in the mid-1930's. The realization that viruses are essentially bits of information-carrying nucleic acids came only 13 years ago.

The first vaccine to be developed following the discovery of viruses at the turn of the century was the yellow fever vaccine in 1937. Incidentally yellow fever was recognized in 1901 and was the first virus disease of man to be discovered. Theiler showed in 1930 that yellow fever virus was pathogenic for mice by intracerebral inoculation. He later passed the virus serially in mice and demonstrated that the resulting strain could be used as a vaccine, first with rhesus monkeys and then with man. Still later on the virus was grown in chick embryos for vaccine production. Yellow fever vaccine is important because the disease is endemic in large portions of continental tropical South America and Africa although it has not been reported in the United States since the early few years of this century.

The demands of World War II brought about the development of vaccines against influenza and Japanese B encephalitis in 1943. Since I participated in these developments during my days at the Rockefeller Institute in Princeton I should like to quote from a lecture about this research on influenza that I gave before the New York section of the American Chemical Society in 1946.

> "With the advent of the war we sought to determine how the special talents of our laboratory could best be used in support of the war effort. There appeared to be several problems concerned with the development of means of protecting people against certain virus diseases. One of these was influenza. The influenza pandemic of 1918 was one of the three greatest outbreaks of disease within the knowledge of man and the only one caused by a virus. It has been estimated reliably that in this outbreak of disease about 500,000,000 people had influenza and of these about 15,000,000 died. At the height of the pandemic people were dying at the rate of one out of every 50 persons in the world per month, a death rate that is unsurpassed in history. In the United States alone 500,000 persons died in four months. Thus the destruction of human life by influenza within a 4-month period was greater than our losses during the years of this greatest of all wars which has just been concluded. I have never been able to understand mankind's resigned and complacent acceptance of such a major catastrophe as the 1918 outbreak of influenza. True, the cause of influenza was unknown in 1918, but one would think that such a calamity would result in a great public demand for a concerted effort to discover the cause of the disease and to develop methods of protection. But this great destruction of human life was accepted almost as ancient peoples accepted natural catastrophes as acts of the gods, and hence beyond the control of man. With the discovery of swine influenza virus by Shope in 1931 and human influenza virus by Smith, Andrewes, and Laidlaw in 1933 one might have anticipated a great surge of activity – but again this was not the case. These significant events passed unnoticed, except for a few virus workers. These few individuals continued their research work on influenza virus with an effort which, measured in dollars, would probably not exceed the cost of a single bomber. Yet, despite the important advances which were made, no means of protection against a major outbreak of influenza was available in 1941. As you may know, the sulfa drugs and penicillin have not been found effective against influenza. Thus, with the advent of war, the mixing of populations, and the accompanying strains and stresses, the possibility of a major influenza epidemic loomed as a dreaded specter. The occurrence during the war of an influenza epidemic of the 1918 variety would have caused untold damage to our war effort. Because of the great importance of the problem and especially because of our background of experience with viruses, we accepted the influenza problem. During the war our major effort was expended in studies on influenza viruses and in the

development of an effective vaccine. In addition, minor assistance was afforded Colonel A. B. Sabin in his development of vaccines against Japanese Type B encephalitis and dengue.

> "Although influenza virus had been known for ten years, in 1941 there was controversy over so simple a property as the size of the virus. Some experiments indicated that the size of the virus was about 100 mμ, whereas other experiments indicated that the size was about 10 mμ. Then, too, there was no unanimity of opinion regarding the conditions necessary for the optimum production of virus, despite the fact that the virus was being grown in chick embryos in several laboratories. The accuracy of methods for titrating virus was unknown and little or nothing was known about the conditions necessary for the maintenance of the immunizing potency of the virus. Because of this general situation and because of our almost complete lack of experience with influenza virus, it became obvious that we should confine our initial work to rather basic and fundamental studies on influenza virus. The fact that others were using a more or less empirical approach made it all the more imperative for at least one laboratory to engage in basic studies. Thus, although we were interested in the development of a vaccine and despite the urgency of the problem, we nevertheless devoted practically all of our first year's work to fundamental studies on influenza virus."

This work resulted in the development of a highly purified concentrated formalized centrifuge-type influenza vaccine which was accepted by the Armed Forces in 1945. In addition a method for accurately measuring the potency of the vaccine was developed. This procedure was accepted by the U.S. government as the official method and it remains so today. The vaccine proved effective in use by the Armed Forces and public until 1947 when a major antigenic alteration occurred in influenza virus and this rendered the vaccine ineffective against the new strain. The new strain of virus was soon incorporated into the vaccine and this vaccine remained effective until 1957 when another major antigenic alteration occurred. The realization that major antigenic changes in influenza virus seemed to occur about every 10 years resulted in the setting up of a world-wide surveillance system for emerging new influenza virus strains. A major test of this system came this past winter with the emergence of the Hong Kong strain. The first report of an influenza epidemic in Hong Kong came near the end of last July and within a month tests indicated that the virus was sufficiently different to render current vaccines ineffective against the new virus strain. Several isolations of the new virus were obtained at once and studies on it were started in the United States. By the first part of September several pharmaceutical companies in the United States started crash programs to produce a Hong Kong influenza vaccine. Two months later several lots of vaccine started to reach the public and by the end of the year the Surgeon General announced that 13 million doses of vaccine had been cleared and released to the public. This major achievement by our pharmaceutical companies is largely unrecognized by the general public.

Although the illness caused by Hong Kong influenza virus has proved to be much milder than that caused by the 1918 strain, increases in the death rates from respiratory infections of children and the elderly did occur this past winter, and I am sure the use of the vaccine did reduce the severity of the attack by Hong Kong influenza. The Hong Kong influenza episode demonstrates that our surveillance system is effective and that our pharmaceutical industry is capable and can be expected to be able to cope with similar situations in the future. However, I continue to be amazed at the lack of acceptance of influenza vaccination by the general public since there is ample proof that the vaccine is effective. The disease is very toxic and frequently causes fatal sequential complications in the very young and the elderly.

An advance of the greatest importance was made here at the Children's Hospital in the 1940's by John Enders and his associates in their researches on tissue culture. Their discovery in 1949 that polio virus could be grown in extraneural human and simian tissue culture led directly to the development of the killed polio vaccine by Salk in 1953 and to the live polio vaccine by Sabin in 1959. Preparations of each of the three types of polio virus are grown in monkey kidney cells in tissue culture and the virus is then inactivated by formaldehyde and in some cases concentrated and purified by centrifugation for use as a killed polio vaccine. In the case of the live polio vaccine, strains of the three types were attenuated by passage in monkey kidney cells and selection for reduction of virulence for the central nervous system of primates. The live attenuated virus types are usually administered orally on sugar cubes. There was a drastic reduction in the incidence of polio following the introduction and use of these vaccines. The live attenuated vaccine is used widely in the United States today and poliomyelitis has been virtually eliminated.

Another major advance was made by John Enders and his associates in their work starting about 1954 with measles virus which they passed first in cultures of primary human kidney cells, then in human amnion cells, then in the amniotic sac of chick embryos and finally in tissue cultures of chick embryo cells. They showed that the chick cell adapted virus could serve as an effective vaccine in the live attenuated form or in the formalin-inactivated form. The pharmaceutical industry selected the live attenuated form for production and in 1963 this vaccine was licensed for use by the public. There was substantial use of the vaccine in 1964 and by October 1966 over 20 million doses had been administered in the United States. There has been a dramatic reduction in the incidence of the disease in the United States every year since the introduction of the vaccine. The central nervous system involvement following measles which was so feared in the past is no longer a threat. The development of the live measles vaccine represents another major triumph.

A live attenuated mumps virus vaccine was developed by Hilleman and associates and licensed for general use by the public in January 1968. The virus used in this vaccine was first isolated by Doctor Hilleman from his daughter during an attack of mumps. It was attenuated by tissue culture passage. Mumps virus was grown in the yolk sac or anmiotic cavity of the chick embryo by Levens and Enders and by Habel in 1945; hence, an unusually long time intervened before production of a commercial vaccine. During the past 14 months over 2 million persons have been vaccinated against mumps in the United States. Continued and expanded use of mumps vaccine should reduce or eliminate deaths from mumps which have averaged 46 per year during the past 10 years and the cases of deafness which can follow an attack of mumps should also be reduced or eliminated.

Although rubella or German measles is not a serious disease of children, a real threat occurs when the disease occurs in women during the first trimester of pregnancy when the risk of fetal damage is high. Rubella virus was first grown in tissue culture in 1962 by Parkman, Buescher and Artenstein and by Weller and Neva. Different strains of rubella virus are now being grown in different cells in tissue culture and are being tested as live attenuated vaccines. The results to date are so promising that a rubella vaccine will probably be licensed next month.

Respiratory syncytial and the parainfluenza 1, 2 and 3 viruses are the most important viral respiratory pathogens of infancy. Since these viruses can be grown in a variety of cells in tissue culture, vaccines will doubtless be developed in the near future. The same situation is found for varicella or chickenpox and here a vaccine will soon be ready for clinical trials. Thus the major childhood diseases known to be caused by a virus can either now or in the near future be controlled by vaccines.

However, there is a malady of children which is most important to the Children's Cancer Research Foundation and that is cancer. I feel that I should discuss childhood cancer in the context of this lecture because of firm evidence that almost all kinds of animals have cancers caused by viruses and increasing, but still not conclusive, evidence that human leukemia is caused by a virus or viruses. This is no new idea, for in 1956 at the Third National Cancer Conference I stated, "Basic biologic phenomena generally do not differ strikingly as one goes from one species to another, and I regard the fact, now proved beyond contention, that viruses can cause cancer in animals to be directly pertinent to the human cancer problem. . . . Cancer is basically a problem in growth, and there is no reason to believe that the growth of most human cells is different basically from the growth of most animal cells. Acceptance of the viral etiology of human cancer as a working hypothesis will involve a marked change in attitude on the part of many investigators, but this is necessary if the right approach and the right design of experimentation are to result. What we do depends in large measure upon what we think." The circumstantial or indirect evidence that has accumulated since that time is substantial and is most impressive in the case of human leukemia.

Since 1957 Type C particles similar to those seen in murine or avian leukemia, about 100 mμ in size and containing a central core of RNA, have been seen in preparations from human leukemia with increasing frequency. Immunological techniques have been developed by means of which these Type C particles have been associated with the disease. It is unfortunate that, to date, there is no confirmed evidence that these particles can be propagated in cell culture for possible vaccine production since killed vaccines have already been shown to protect mice against murine leukemiogenic viruses. However, these particles appear to be so similar to those viruses which cause leukemia in chickens, cats, dogs and mice that much more research on them is warranted. Of greatest interest would be their propagation in cell culture for this would open up a variety of new approaches related to their identification as disease producing agents and to vaccine production.

Another particle found with great frequency in lymphoma and in myeloid and lymphoid leukemia is a Herpes Type Virus (HTV) about 120 mμ in size and containing a central core of DNA. This HTV particle is found in the Burkitt lymphoma and in mononucleosis. Dozens of human cell lines containing the HTV particles are now being grown. In some cases the percentage of cells containing HTV particles has been increased many-fold by selection and passage. The HTV can be concentrated and purified and such preparations show no cross reaction serologically with herpes simplex or zoster virus. The immunological evidence relating HTV to the disease in the cases of the Burkitt lymphoma and mononucleosis are excellent and perhaps only fair in the case of myeloid or lymphoid leukemia. There is some evidence that the addition of HTV particles to lines of normal human cells causes changes in such cells. There is also preliminary evidence that HTV particles can cause disease in animals. Needless to say, the tempo of research activity with HTV is presently at a very high level with much remaining to be done. We can only await the outcome with great interest.

Despite the successful work with vaccines in the case of murine leukemia it does not follow that proof of a relationship between viruses and human malignancy will lead directly to control of cancer by vaccines. Viral vaccines are successful because of the protein-component of the virus which is antigenic and responsible for viral antibody production. Work with some viral cancers of animals indicates that cell-to-cell transmission of naked viral nucleic acid may be responsible for the progression of the cancer. Since nucleic acids are very poor antigens such a situation in the case of human malignancy would not be expected to yield to vaccines as we know them today. We may have to depend upon further significant advances in a field to which The Children's Hospital, under the able direction of Dr. Sidney Farber, has already contributed so much, namely cancer chemotherapy – or possibly to an exploitation of the discovery by Hilleman and associates at the Merck Institute that double-stranded ribonucleic acid induces the production of interferon, a material remarkably effective against viruses.

Doctor Chamberlin in the Virus Laboratory has for some time been studying the physical chemical properties of a variety of double- and triple-stranded RNA and DNA as well as hybrid polymers. Because such a wide variety of polymers was at hand, he and Doctor Colby decided to study the specificity of interferon induction in chick embryo cells by these polymers. They found, as had Hilleman and associates, that a double-stranded polymer consisting of polyriboinosinic acid and polyribocytosinic acid (rI:rC) was most active and other RNA-like polymers somewhat active in the induction of interferon. Activity was not found unless all of the sugar residues were ribose although the effectiveness of the different active polynucleotides at a given concentration varied considerably. The difference in activity did not appear to be due to differences in the rate of uptake, which by the way was influenced favorable by DEAE dextran, or to differences in the rate of breakdown within the cells. The high degree of specificity of the induction process led Chamberlin and Colby to suggest the existence of a specific intracellular receptor site for the double-stranded polyribonucleotides, probably a protein. Enough information has already been obtained to warrant intensive research with interferon inducers for, despite some present problems of toxicity, they might prove effective against cancer in which mature virus particles are involved as well as cancer in which the cell to cell transmission of naked nucleic acids is involved. There are preliminary reports of effectiveness against some animal cancers. Interferon inducers also offer hope of prophylactic control of those diseases caused by viruses having many serotypes, such as for example, the common cold.

The opportunities that exist today for significant advances in biomedical research are so great that one can look to the future with great expectations. Let us hope that long before The Children's Hospital Medical Center celebrates its next Centennial the control of diseases of children will be such that the activities of the Center will be far different from what they are today. I salute the great work of the Center in the past and in the present and I predict that the future will find the Center even greater and more effective in its work with children.

THE IMPACT OF IMMUNOLOGICAL PROGRESS ON THE PEDIATRICS OF THE FUTURE

Gustav J.V. Nossal, Ph.D.

The Walter and Eliza Hall Institute of Medical Research,
Melbourne, Australia.

I am more than sensible of the great honor that you have accorded me by allowing me to join you for the centennial celebrations of your famous hospital and medical center. In Australia, we regard Boston as one of the two Meccas of clinical medicine, the other being London. The Children's Hospital, by its tradition of excellence in patient care and its many distinguished research contributions, is a continuing vindication of this viewpoint. I have been asked to take as my subject the question of how the current immunology research explosion will affect your next 100 years. This task is more risky but also more interesting than to look just 10 years ahead, as it is already quite clear that the next decade will see spectacular progress in organ transplantation and immunosuppression generally. The longer view, however, can be taken only in a more general context and thus we must begin with a few remarks about the overall march of science.

Time Cycles in Practical Progress.

The link between basic research and practical progress is both very real and very capricious. We are passing through an age where the links have been so close and obvious that we have almost forgotten the latter point. Harvey, Newton and Mendel, to name just three, were pretty good scientists but a direct pay-off from their work was a long time in coming. In biology, no worker in history has had a greater impact than Charles Darwin, yet a century had to pass before the principles of mutation and selection gave us vastly improved crop seeds – and more potent biological warfare weapons. In our generation, we have been spoilt. We have come to expect, in turn, vitamins, hormones, antibiotics, open-heart surgery, anti-viral vaccines, neuro-active drugs and organ transplants as annual dividends and the men and institutions supported by research dollars as blue-chip stocks, assured of steady capital appreciation. There is a danger in this assessment. Medical science is much too complex and multifactorial an entity to obey simple exponential kinetics. It seems to me certain that in the century ahead our power to prevent and treat disease will continue to grow, but equally inevitable that the pace of that growth will be highly irregular and unpredictable. It is part of the duty of our profession to explain this to the community and to our political leaders. Your nation has reason to be very proud of its administration of public research funds in the last 20 years. The activities of bodies like the National Institutes of Health and the National Science Foundation have served as examples to many nations. Yet I fear that some of the same voices in Congress that set in motion your formidable post-war effort in medical research are now saying, somewhat plaintively: "You solved polio pretty quickly when you didn't have much money – now, when you have so much more, why are you being so slow about cancer and heart disease?". This new attitude, and the fiscal problems which are, at least in part, attributable to it, is our own fault. We have failed to communicate, and perhaps even to face up to, the importance of viewing medical research in an appropriate time dimension. We cannot and should not assume that the next century must produce advances as important statistically to pediatrics as the last. What we must stress is that a valid experimental observation has a quality of permanence unmatched by any other human achievement. Interpretations will change, elaborations will ensue, the sub-structure of the relevant science will evolve, the discoverer will be proven wrong in innumerable ways and will be forgotten; yet his experimental contribution is one of the bricks without which the edifice could not be built. In pediatrics, the next major therapeutic advance may come soon or only after years; but, when it comes, it is a gift to the whole race, for as long as it survives in civilized form. It is this historical quality of research that provides at once its major thrill and the chief justification for its financial support. It is armed with this type of argument, and not with emotional, sensationalistic or over-optimistic claims, that our profession should approach the legislature in the century ahead. With the foregoing provisos, I view scientific progress in that century with great optimism. The real breakthrough has already come, and that is widespread community acceptance of the scientific method as the best approach to problems. In this atmosphere, a new one unique to our century, pediatrics cannot fail to prosper.

Immunology as a key interdisciplinary science.

Where will immunology fit in? This science has had a peculiarly interdisciplinary quality since its inception. Edward Jenner was a general practitioner, Louis Pasteur a bacteriologist, Elie Metchnikoff a zoologist, Karl Landsteiner a chemist, and Paul Ehrlich could be described as a "professional all-rounder". While the impetus during those early days was naturally and properly directed chiefly towards the understanding of antibodies and the prevention of infectious diseases, the relevance of the subject of immunology to genetics, hematology and cell physiology was soon recognized. However, it is probable that no one predicted the degree to which immunology would invade other sciences during this present decade, the dawn of the "second golden age" of immunology. Now its exponents will be found in any one of the departments of a medical school, and in science departments as diverse as zoology, biophysics and even statistics! I believe there are three chief reasons for this infiltration. The most obvious is the fascinating emergence of the clinically important fields of transplantation, auto-immune diseases and cancer immunology. The second is the fact that the methodology of immunology has wide applicability in many completely unrelated research areas. The third, and perhaps most important, reason is more complex. It could be described as an inchoate yet widespread feeling that after the triumphs of molecular biology, the cracking of the genetic code, the next big leap forward must be related to multi-cellular organisms, preferably mammals, and must offer insights into how the cells of such organisms work, interact and go wrong. The exquisite sensitivity of immunological techniques and the challenging intricacy of the behavior of lymphocytes, added to the inherent importance of the body's defence system, make immunological phenomena a choice target for a broadly-based, multi-disciplinary attack. In this search, it is early days and the lymphocyte still retains most of its secrets, but one lesson of immense potential importance has already emerged. Fears are often expressed that the information explosion will rend the fabric of science, and that we will be left with nothing but a whole tribe of super-specialists, each knowing more and more about less and less. Instead, modern immunology has created an army of some thousands of scientists, each naturally possessing one or more special interests, but each sufficiently dependent on all the others that the need to communicate has remained urgent. Thus each specialist is at least a bit of a generalist. He has learnt to live in, and has demonstrated the feasibility of, a multi-disciplinary scientific world. In so doing, he has kindled a like desire for a more general involvement in many other types of scientists.

Immunology in Pediatrics.

Organ transplantation has so far made relatively little inroads into pediatrics. Will this change in the century ahead? The essential reason for present skepticism about transplants for children is a mistrust of the immunosuppressive drugs used. We rely now on three products: corticosteriod drugs, azathioprine and anti-lymphocyte serum. Each of these has undesirable properties which confer toxicity, and none of the three, singly or in combination, is 100 per cent effective in warding off the immune attack mounted by the patient against his graft. Confronted by the prospect of a life-long regime of relatively toxic drugs to support an often sub-optimally functioning grafted organ, the pediatrician naturally hesitates, perhaps more so than the physician looking after a forty year old mother of three. Considering that two of the three currently used therapeutic agents have emerged within the last five years, it seems certain that the years ahead will supply us with more effective and less toxic immunosuppressives. However, even the ideal drug would not solve the pediatrician's dilemma. Almost by definition, the prolonged administration of immunosuppressives would leave the patient's defences weakened, allowing the emergence of virulent and frequently bizarre infections, and perhaps permitting a heightened incidence of malignant disease. Thus, our pediatrician will, without doubt, look to another principle to ensure the long-range health of both graft and patient.

Immunological Tolerance.

This principle is already in existence in the laboratory. A formidable array of practical problems remains to be solved before it can be applied to man, but all of these will be eliminated well before 100 years. The principle is that of immunological tolerance. Simply put, the induction of immunological tolerance is the exact opposite of a vaccination. In a vaccination, we increase the defense potential of an individual specifically against a particular micro-organism. Antigenic molecules in the vaccine cause antibody formation and immunological memory against one pathogen, without in any way heightening the recipient's ability to deal with unrelated microbes. In the induction of immunological tolerance, special circumstances are created whereby antigen molecules so modify a recipient's immune system as to reduce or abolish his capacity to react to the antigen when he meets it at some later time. The immune defect is a specific one: an animal made tolerant towards antigen A can respond quite normally to antigens B, C, D etc. Herein lies the vital difference between the principle of tolerance and that of immunosuppression. The experimental circumstances needed to induce tolerance are various. At first it was thought that tolerance could only be induced by exposure of an animal to antigen during embryonic or early post-natal life. It is now clear that tolerance can also be induced in adult animals, provided stringent requirements of antigen dose, antigen molecular weight and antigen persistence are met. The technical details need not delay us here. Suffice it to quote one concrete example of tolerance induction in adult animals, arising from the work of my colleague Dr. G.L. Ada and his students at the Walter and Eliza Hall Institute.

The protein constituent of the organs of locomotion of bacteria is a molecule termed flagellin. This is a powerfully immunogenic molecule; one-thousandth of a microgram injected on a single occasion can cause a rat to form antibody. Flagellin from Salmonella bacteria has a molecular weight of about 40,000. Chemical degradation of a rather simple form can yield a fragment of molecular weight 20,000 which retains all the antigenic grouping of the whole, native molecule but which is less powerfully immunogenic. When this lower molecular weight, "blander" antigen is injected repeatedly into healthy, normal adult rats, without the help of any immunosuppressive drugs, the treated animal gradually loses its capacity to respond to the flagellar antigen, even when this is now given in immunogenic form. After four weeks of daily injections, appropriately treated rats give a drastically reduced response to whole flagellin, even when this is given in optimal dose and together with a powerful adjuvant substance.

So far I have said that to induce tolerance, the flagellar antigen must be given in a low molecular weight form, the 20,000 mol. wt. fragment, and over a prolonged period, i.e. 4 weeks. However there is a third and even more important consideration, and that is the size of the daily antigen dose. It turns out that there are two distinct zones of antigen dosage capable of inducing tolerance. One can either use daily amounts of relatively large quantities of antigen, e.g. 100 μg. This induces so-called "high zone tolerance". Alternatively, one can use minute (I am tempted to say homeopathic) quantities of antigen, e.g. 10^{-7} μg per day, or one billion times less, which causes the induction of "low zone tolerance". Doses in between these, e.g. in the region 10^{-5} to 1 μg, fail to cause tolerance. Instead, they may even cause some antibody formation.

The theoretical basis of these extraordinary findings are still the subject of intense debate, and much work remains to be done. However, some conclusions with obvious practical implications emerge clearly.

1) Given appropriate circumstances of antigen dose, molecular form and timing,

one can induce tolerance towards even very powerful antigens.
2) This can be achieved in adult animals and without toxic drugs.
3) This need not necessarily involve large and possibly toxic doses of antigen; it can be achieved with quite minute amounts, provided these can be kept up for some weeks.

Practical Implications of Immunological Tolerance.

Looking 100 years ahead, it is perhaps permissible to glide over the many technicalities involved in the purification and testing of antigens, and to examine the ultimate implications of the discovery of high and low zone tolerance for pediatrics and medicine. In the field of organ transplantation, these include better functioning grafts, with lowered and eventually no administration of immunosuppressive drugs, and a consequent elimination of the vast majority of complications of transplant procedures. With better understanding of the genetics and chemistry of the antigenic molecules in organ transplants, the so-called histocompatibility antigens, one might well be in a position to manufacture these tolerance-inducing antigen fragments synthetically, thereby eliminating the logistic problems involved in purifying antigens from a cadaver. This goal sounds far fetched in 1969, but no more so than did sending a man to the moon in 1957. There are no obstacles of *principle* standing in the way; only a terrifying range of practical problems which we must patiently work through, one by one.

One problem of special importance to pediatrics is allergy. Admittedly the nature of allergenic molecules is a difficult and complex question. Nevertheless, if the allergist and the immunologist realistically link hands in the decades ahead, much progress must ensue. The induction of low-zone tolerance to allergenic molecules, by desensitization programmes placed on a vastly more scientific footing than today, should prove feasible. Moreover, we have only recently discovered that the antibodies responsible for allergic states belong to a special chemical class, which we term IgE. We know practically nothing of the cellular and biochemical rules governing IgE production, but we now have the tools necessary to find out. I believe the pediatrician active at your second centennial will have much greater power to treat his allergic patient scientifically.

Of the auto-immune disorders, the most important to pediatrics are probably the various forms of renal disease. It is becoming apparent that a great deal of non-infectious renal disease is immunological in nature. Two broad types of kidney injury can be recognized. In one, the kidney is the true target of an antibody attack; the patient, for reasons that are still wholly unclear, makes antibody to constituents of his own kidney substance. In the other and more common variety, the kidney is an innocent bystander. It is the victim of its own profuse and specialized capillary blood supply. In these so-called "immune complex" diseases, soluble antigen-antibody complexes form in the blood-stream and sludge out in the kidney glomeruli, where they fix complement and cause irritant damage. So far we are not particularly clever at curing either of these forms of immunological disorder, but the probings of today's immunologist must help tomorrow's pediatrician.

An occasion such as this may be an appropriate one to express one's wonder at the ever increasing number of diseases in which an immunological etiology is known or suspected. Ten years ago, auto-immunity as a concept was confined to a few rare disorders such as acquired hemolytic anemia, systemic lupus erythematosus, and Hashimoto's thyroiditis. Today, it figures as at least a possible cause of much of chronic renal and liver disease; of perhaps the bulk of non-neoplastic endocrine disease, including myxedema, thyrotoxicosis and Addison's disease; of conditions as diverse as pernicious anemia and myasthenia gravis: one wonders where it will all stop! In this connection, I feel we should take note of some preliminary but highly exciting work of Dr. Roy Walford of California. He has implicated immunological activity and auto-immune processes amongst the causes of ageing. Mice given immunosuppressive drugs during their life lived 20 per cent longer than untreated individuals. Knowing that the vascular tree is a prime target for immunological events, e.g. in kidney graft rejection, one wonders to what extent the killing diseases of man, atherosclerosis, arteriosclerosis and hypertension, may be associated with immunological activity. A finding of relevance is that germ-free mice live 3 to 4 years, a year or more longer than conventional mice. These animals, of course, are shielded from more than just immunological events, and many plausible causes of longevity can be put forward. Nevertheless, their immunological virginity may be an important factor.

The above speculations are probably outrageous, but more serious attention must be given to relationships between malignancy and immunology. Here two key findings are a) that many tumors induced by experimental animals carry tumor-specific antigens and b) that many carcinogenic agents are also immunosuppressive agents. It is thus possible that the body's immune apparatus normally tries to defend itself against altered, pre-malignant cells, and that clinical malignancy results only when this line of defence, for one reason or another, breaks down. If this is true, our pediatrician of the future must concern himself with ways and means of bolstering the immune potential of the child with cancer.

One recent line of investigation of special relevance to pediatrics should be mentioned. At least five teams of workers have now shown that leukemia viruses of mice have a profound depressive effect on the immune capacity of the host, and this defect makes itself felt quite early in the oncogenic infection. Does the leukemic child exhibit a similar defect, and if so, is this a cause or contributory factor to the spread of the malignant process?

Immunodiagnostic Methods in Pediatrics.

Let us return from lofty questions of life and death to more mundane matters of day-to-day pediatrics. A very great proportion of childhood illness is mild infectious disease. Today, the search for the infectious agent is too tedious to be worth the effort in many cases. Here, the great sensitivity of immunological techniques will help us in the future. On theoretical grounds, a throat swab or nasal washing contains quite enough antigenic material for identification by immunofluorescent techniques. The routine pediatric clinic 100 years from now may well contain an automated immunofluorescence analyser which would identify pathogens within 30 minutes. In fact, immunoassays for a host of substances present in small quantities in blood or urine will also be as routine as flame-photometric measurement of electrolytes is today.

Chairs in Immunology.

Even allowing a degree of bias on my part, you will admit that immunology will play a vital role in the biology and medicine of the future. Yet its teaching in our universities still lacks cohesion. Immunology classically is taught as a part of microbiology, and snippets of the subject find their way into courses of biochemistry, physiology, pathology, medicine, surgery and other subjects. To a degree, this dispersion is a natural outcome of the many ramifications of the subject, and in itself may not be a bad thing. Chairs and departments of immunology are still rare in our medical schools, especially in the smaller and less renowned ones. This creates the danger that no man or body of men in the school will have the breadth and perspective in the subject to ensure its adequate overall coverage in the medical curriculum. Even if he had the required knowledge, the immunologist in, say, the department of medicine might lack the authority to "push" his discipline against competing claims of established, full departments. Some years ago, the World Health Organization made a detailed study of this question and published an eloquent plea for the establishment of independent chairs of immunology in universities and medical schools. It is a view with which I fully concur but which appears to have gone largely unheeded. Chairs of ophthalmology, otorhinolaryngology, dermatology, anesthesiology and radiology are proliferating at a great rate. Those in immunology are still all too rare, yet few would argue that the former disciplines are inherently more important that the last.

Conclusions.

If peering into the future has any value other than its being an amusing game, it is only to the extent of our willingness and ability to shape that future. In medicine, we are in a better position than most groups to design our destiny. We delve into realms that, despite the era of big science, still savor of the arcane, thus few in authority dare contradict us. Individually, if not always collectively, we enjoy the community's good will and their recognition of our importance. Economically, we represent one of the world's major industries. Organizationally, we have powerful means to prevent an excessive degree of governmental control. All of these factors impose a great responsibility on the leaders of our profession to plan wisely. I believe that research, both fundamental and clinical, must play a continuing and even an increasing role in that planning. As Dr. Joseph Cooper has recently pointed out, the current N.I.H. research cuts, with their world-wide repercussions, may have some beneficial effects *if* they do not last too long. It is only fair that research should compete openly and distinctly with medical education and community medical care for public dollars. However, I consider it extremely important that the gloom inevitably cast by these (hopefully) short-term measures does not escalate into a profession-wide disenchantment with research and a consequent disengagement of many from the academic way of life and thinking. To me, the immunology research explosion has presented one telling paradox. It has opened a thousand doors, but it has shown us that the inner recesses of all those thousand rooms are very dark. We know enough about immunology to prevent graft rejection and vaccinate mice against tumors; we do not know the reply to obvious freshmen questions such as whether one lymphocyte possesses the information to form one antibody only, or whether macrophages are really important in antibody production. The paradox, in altered form, will strike the worker of 100 years hence also. New insights gained will spawn new and often quite fundamental questions; knowledge and ignorance will advance in close parallel formation. An inevitable product of this paradoxical reaction will be power; in the present context, power to manipulate the mammalian immune system in health and disease. This power, the pediatrician 100 years from now will need, and will have a right to expect. We will help him by keeping our research effort in honest perspective, by both setting and selling more realistic goals. Research in immunology must continue to receive high priority. It will eventually help to lead us to a richer understanding of growth, differentiation and ageing; of organ transplant acceptance; of many sub-acute and chronic diseases of as yet unknown etiology, and of the cancer process. If so, this second golden age of immunology may, to our pediatrician of 2069, seem even more historic than the Pasteurian era.

Acknowledgements

Contracts and grants from The National Health and Medical Research Council, Canberra, Australia, the National Institutes of Health AI-0-3958, the United States Atomic Energy Commission AT(30-D-3695), and the International Atomic Energy Agency 470/RB have greatly assisted our work at the Hall Institute.

This is publication number 1337 from the Walter and Eliza Hall Institute of Medical Research.

MOLECULES, GENES

AND

CHILD HEALTH

Edward L. Tatum, Ph.D.

Professor of The Rockefeller University
The Rockefeller University, New York, New York;
Nobel Laureate, 1958

The explosive expansion of biological knowledge and concepts during the past several decades not only justifies calling this the age of molecular biology, but leads us to expect increasingly effective and exciting insights into problems in human biology.

Today, I want to discuss with you the significance, and actual and potential contributions of these new biological concepts in the area of human biology – child health – with which The Children's Hospital Medical Center has been concerned for the last century. Certainly no other area is more important to the welfare and progress of man and society than is the physical and mental health of our children. Although predictions are notoriously hazardous, it does not seem rash to expect perhaps even greater developments in this area than in most other areas of medicine.

I want to try to substantiate this expectation during this lecture, discussing the concepts of molecular biology and their applicability to certain important problems of child health, and exploring possible new developments in research which may lead to understanding, and hence to prevention, treatment, and cure.

First, let me summarize the basic concept and ideas of molecular biology and genetics. They are:

1. That genes, the hereditary units of all life, consist of DNA, and carry all their necessary genetic information in this unique macro-molecule.
2. That this information is encoded in the specific sequence of base pairs in the double helical DNA molecule.
3. That we now know most of the details of the triplet code apparently common to all life and how the code is read and punctuated, that is, begun (AUG triplet) and ended (UAA triplet). We also have learned much about the mechanisms of replication and translation of this unique molecule.
4. That mutation consists in its simplest form in alterations of single base pairs, changing a given code triplet into a different one. In more complex situations, one or more base pairs may be added or deleted. An amino acid triplet may be changed to a stop signal such as UAA, ending the growth of a polypeptide chain at that point. Insertions or deletions of base pairs except in units of three will prevent further meaningful translation of the message for distances roughly proportional to the length of the inserted or deleted areas, or even prevent any further translation.
5. That gene expression in an organism consists in essence of the reading of the triplet code of DNA, and its transcription and translation via RNA into the specific amino acid sequences of the unique protein molecule specified by each gene. It follows from, and is inherent in, this that the unique characteristics of each organism, its potentialities, are ultimately functions of its complement of proteins and enzymes and

their interrelated activities. These *structural genes* thus determine the quality of enzymes or other proteins and hence the potentialities of the organism.

6. Superimposed on this system relating genes to proteins is the concept that different genes – different DNA molecules – are read and transcribed at different rates and at different times, so that different messages are selected and used depending on the needs of the organism, or cells of particular tissues or organs within the organism. Such a selective system of gene activation is generally considered to be involved in differentiation and development.

   This selective process appears to be under the control of *regulatory genes*, which respond to specific cellular environmental factors by regulating the activities of structural genes. In bacteria some regulatory genes have recently been shown to produce specific protein *repressor molecules*, which attach to the corresponding structural genes and prevent their transcription. (Ptashne, Gilbert).

At the chromosomal level gene activity has been correlated with expansion, or "puffing", presumably permitting more effective template functioning of the DNA in mRNA synthesis. At the chemical level, this activation appears correlated with, and perhaps controlled by, metabolic changes in the basic histone associated with chromosomal DNA, such as methylation or acetylation.

The successful delineation of these principles of molecular biology has involved two broad generalizations. One emphasizes the significance of molecules, simple to complex, in life processes. Here the specificity of the living cell is dependent on, and understandable through, specific molecular structures, genic DNA, messenger and transfer RNA, enzyme and structural proteins, polysaccharides, fats, vitamins, amino-acids, etc. The other generalization stresses the dynamic aspects of these structures and molecules, that each is related to the other in an orderly sequence of specific interactions, each step of which is understandable in terms of chemical reactions and affinities of the molecules concerned.

When dealing with a simple phenotype, such as a deficiency in amino-acid or vitamin synthesis in mutant strains of microorganisms, the analysis of reaction sequences and the definition of gene function in terms of enzyme activity is relatively simple and straight forward. It becomes difficult when the phenotype is more complex as in morphological and biochemical differentiation of cells or tissues, or at the higher organismic levels of behavior and mental activity. However, there is hope of successfully unravelling these more complex phenotypes. This hope rests on the premise that these phenotypes are also gene controlled and also basically involve molecular specificities and sequential functional relationships. The analysis of such a complex phenotype then becomes in principle one of starting at both ends of the sequence, gene and phenotype, and trying to reconstruct the entire sequence in terms of molecules and their interactions.

In looking into the developments and experimental approaches now underway in problems related to child health, I (as a microbial biochemical geneticist), am particularly impressed with the increasing extent to which the techniques and concepts of microbial genetics and molecular biology are becoming involved. In reviewing some of the exciting possibilities of this involvement, I want first to outline these techniques and concepts of microbial biochemical genetics, which over the past 20 years have provided the foundations on which molecular biology has been developed. I will then return to the counterpart developments and applications in the mammalian or human situation.

An essential first step in investigating and understanding gene functioning came with the production in the laboratory of strains of microorganisms with different single gene mutations, each of which was deficient in the ability to carry out the synthesis of an essential molecule, such as a vitamin, amino-acid, or nucleic acid base. This led directly to the generalization "one gene: one biochemical reaction", soon modified to "one gene: one enzyme" and then to "one cistron: one polypeptide chain". I am sure I need not elaborate on the applications of such mutant strains to the analysis of complex biosynthetic sequences, and to the analysis of more complex phenotypes in terms of a single defective enzymatic reaction. The major point to keep in mind is the tremendous experimental advantage of being able to compare strains of normal cells with strains differing at only a single gene locus.

Thus, the study of gene function in microbes through the use of mutants has led to the clarification of the consequences of mutational interruption of metabolic steps in terms of depletion of a required end product, or of accumulation of intermediates, and suggests means of avoiding the undesirable consequences in both instances. It is also leading to a beginning of understanding of means of modification and regulation of both gene and enzyme activities through feed-back mechanisms, and through specific gene repressors and inducers (depressors).

Along related lines, the phenomenon of cell-fusion and establishment of "heterocaryons" in certain microorganisms has permitted experimental studies of gene function in terms of "dominance" and "complementation".

A major experimental advantage of microbes in comparison with more complex multicellular organisms is that the vast numbers of cells involved make possible selection and establishment in culture of even a very rare desired type of induced mutant.

Finally, mutant strains of microorganisms have provided means of detecting and studying hitherto unsuspected and unusual mechanisms of transfer of new genetic material from cell to cell, as in chromosome transfer in bacterial sexual recombination, in gene transfer via virus infection in transduction, or in DNA molecule transfer in transformation. Even rare events such as gene or DNA transfer can be detected and new strains recovered by suitable selective techniques, just as for a rare mutational event.

Let us examine the significance and applicability of these general microbial concepts and techniques to the mammalian situation, particularly in reference to human hereditary metabolic errors. Actually, the realization that some human hereditary problems were due to single specific metabolic defects considerably antedated work with microorganisms, with the reports of Garrod on PKU, alkaptonuria, albinism, etc. The significance of Garrod's classic findings, published near the beginning of this century, was largely unrecognized until much later.

PKU is a classic example of a complex hereditary phenotype, including mental retardation, in which the comparison of normal with single gene mutant individuals has permitted pinpointing the single metabolic lesion in a single enzyme. The absence of phenylalanine hydroxylase leads to the accumulation of phenylalanine and its injurious metabolites such as phenyl pyruvic acid. Many examples of this type of relationship between single genes and metabolic errors in man now document the basic similarity of gene action in man and in microbes and give us confidence in the success of analysis of all single gene controlled metabolic errors in man. The list is already too long to enumerate here, but includes, among other diseases of children: galactosemia (UDP- galactose transferase), maple syrup urine disease (branched chain amino acid decarboxylase) the glycogen storage diseases, and the even more complex Lesch-Nyhan syndrome (hypoxanthine-guanine phosphoribosyl transferase – HGPRT). In further analogy with microbes, these and many other human enzyme defects are shown by cultured cells.

The possible application of concepts of molecular genetics to therapy of such human problems leads to the much speculated upon subject of *biological engineering* – which we may divide into several categories. Eugenics, or *eugenic engineering*, would be defined as avoiding the recombination of deleterious genes present in the population. Its success will depend on *a*) The capability of detection of heterozygous carrier individuals, and *b*) The social decision of any two such parents not to reproduce. Given these conditions, genetic counselling could be very effective in reducing the incidence of such conditions as PKU, galactosemia and cystic fibrosis. The newer techniques of human cell culture, when combined with sensitive specific enzyme tests or cytological observations, in some instances are making the diagnosis of carrier heterozygous individuals much more simple and certain. Bearn and coworkers have found that cultured cells either homozygous or heterozygous for CF, or for other genetic mucopolysaccharidoses develop metachromatic granules which differentiate them clearly from normal cells. With sex-linked characters such as a G6P-dehydrogenase deficiency, or the HGPRT deficiency (Lesch-Nyhan syndrome) the Lyon phenomenon of random X inactivation permits identification of a carrier by the isolation of both normal and deficient clones of cells. With the use of the new techniques of amniocentesis, combined with enzymatic tests and cytological examination of the resultant cell cultures, it should be possible to determine whether a fetus has no mutant gene (normal), carries one mutant gene (carrier) or is homozygous or hemizygous for the gene (affected). With this diagnosis at 14-16 weeks, a pregnancy can then be easily and simply terminated, either to prevent the birth of affected individuals or even of carrier individuals. The latter choice, if sufficiently exploited, could in one generation essentially eliminate recessive genes such as CF, PKU, galactosemia, etc. from the population. Obviously, complete exploitation of amniocentesis and karyotypic examination could also greatly reduce or even essentially eliminate the occurence of conditions such as mongolism or any other easily diagnosed chromosome abnormality.

So much for possibilities in eugenics. Let us now consider the area of euphenics or *euphenic engineering* or intervention. This can be defined as control of expression of existing genes so as to avoid the appearance of an undesirable phenotype. Here too, the various possible approaches are clearly counterparts, if not based on, microbiological precedents.

The first possibility, replacement of a molecule which is an essential gene product, is already widely used. Actually, all of us illustrate euphenic engineering when we rely on our diet to supply our nutritional needs for vitamins and amino acids. Other examples of hereditary diseases in which therapeutic replacement of missing gene products are used include agammaglobulinemia, hemophilia, diabetes, and growth-hormone-deficiency dwarfism. In theory, supplying a missing enzyme itself, instead of its product molecule, can be visualized. An intriguing technique for avoiding immunological sensitization by administered enzymes is the use of semipermeable microcapsules containing an enzyme solution. Chang and Poznansky have reported the effective administration of catalase in acatalasemic mice by this technique.

The second major category of euphenic engineering is the prevention of accumulation of injurious molecules which are substrates of missing or defective enzymes. PKU has become a classic example of this approach. Dietary limitation of phenylalanine intake limits accumulation of harmful metabolites such as phenylpyruvic acid. If therapy is instigated early enough, apparently many or most of the phenotypic effects of the mutant gene, including brain damage, can be avoided. Analogous therapy appears effective in other diseases, such as galactosemia, and maple syrup urine disease.

Other intriguing possibilities of preventing accumulation of undesirable, injurious products include the design and use of specific drugs to prevent synthesis of the product, or of agents which detoxify it. The effective use of allopurinol to inhibit xanthine oxidase and avoid uric acid accumulation in gout, and the use of penicillamine to chelate excess copper in Wilson's disease, are interesting models illustrating these possibilities.

The third general approach to the control of gene activity also makes use of possibilities suggested by microbial models. One involves end product feed-back repression of enzymes involved in production of undesirable products, as reported for the treatment of orotic aciduria by administered pyrimidines. Another, as yet purely hypothetical in mammals, would involve the isolation and use of specific gene repressor molecules. If all natural repressors turn out to be high molecular weight proteins, as are the two so far studied in bacteria, this would appear to limit the applicability of this approach. Nevertheless repressors could in theory be useful in preventing undesirable metabolic reactions, or to decrease the activity of undesirable dominant genes, as in Huntington's chorea.

Similarly, natural derepressors or "inducers" would be useful in stimulating hypo-active genes, or inactive genes as would be necessary in organ or tissue regeneration.

It is interesting to speculate on the design, synthesis, and use of specific simple molecules as repressors or derepressors. The prospects would seem not too far-fetched when we consider that some antibiotics such as actinomycin combine with DNA and inhibit its template action with some limited specificity for DNAs of different base ratios, and certain non-metabolizable analogues of galactose are gratuitous inducers of β-galactosidase. Hormones, such as the sex hormones, cortisone, or ecdysone, also relatively simple molecules, appear to act by stimulating the template activity of specific genes. Along this same line, we may also think of restoring normal functioning of mutant genes at the translation level of gene activity by specific chemicals as in the "suppressor" action of streptomycin in bacteria (Gorini).

The third major category of biological engineering involves changes in the genetic material itself, which has been referred to as *genetic engineering.* The theoretical possibilities include directed mutation, replacement of a gene by another either isolated or synthesized, or addition of new genetic material to the existing genome. In every case distinction must be made between gene changes in the germ line and in somatic cells. The possibilities of genetic engineering in the germ line seem rather remote, and may come only via somatic cell changes, when and if somatic cells can be induced to behave as zygotes and to develop into complete organisms. In contrast, somatic cells, grown in culture, can be subjected to techniques of gene transfer discovered in microorganisms, such as cell-fusion and recombination, virus-carried transduction, and direct transformation with isolated DNA. A rare cell type with the desired genetic qualities can then be isolated, grown in quantity, and reimplanted into the deficient recipient. The feasibility of this is increased by the probability that with a recessive character it would be necessary to replace or add only one normal gene per cell, and that it might suffice to alter or introduce only a minimum number of normal cells in a single critical tissue or organ to restore a defective phenotype to normal.

Promising beginnings have been made with mammalian cells. Many types of somatic cells can be grown in culture. Selective methods of isolating certain rare induced mutant cells from a cell population have been devised, as for a thymidine kinase deficiency, or GHPRT (Littlefield). Transformation by DNA has been reported in mammalian cell cultures, and tumor viruses appear to carry new gene(s) for malignancy into the invaded cell. Benign virus transfer of desired genes seems a real possibility, a concept supported by Rogers' evidence that a new arginase enzyme persists for years in rabbits or humans exposed to rabbit papilloma virus.

As to the final step, the correction of genetic problems by implantation of cells with desired genes, in some instances this seems to have been successfully accomplished. Good has reported treatment of a lymphopenic agammaglobulinemic boy with bone marrow and peripheral blood from a sister, matched (by the mitomycin technique of Bach and Vaynow) at the major human incompatibility locus, HLA. This locus in man is the analogue of the major H2 incompatibility locus in mice. The transplanted cells survived and became established, and the negligible immunoglobulin A, G and M levels were restored to normal. This therapy is actually analoguous to the cure of *w* mutant gene anemia in mice with cell transplants, and thus in a sense is based on the animal model. In another instance, Bach has successfully treated a case of Wiscott-Aldrich syndrome (characterized by a platelet deficiency and low IgM levels) by destruction of the defective marrow cells with cyclophosphamide and marrow transplants from an incompatibility matched sibling. Thus the prospects appear excellent of successful transplants of cells in the correction of genetic defects, at least of those involving blood or plasma. Perhaps in time this will include sickle cell anemia, thallasemia, and the sex-linked chronic granulomatous disease of children involving failure of release of lysosomal enzymes in leukocytes.

Few, if any, of these various approaches to the understanding, treatment, and correction of hereditary defects in man would have been, or can be, carried to success without the all important techniques of cell-culture. I would even predict that other unanticipated possibilities will arise from observations of cells in culture. For example, the phenomenon of the fusion of mammalian cells in culture with production of heterocaryotic multinuclear cells, has permitted studies on gene dominance and the selection of recombinant cell types. It has at least the potential of detecting the elusive "repressors" and "activators" of genes in mammalian cells, and thus facilitating their isolation, study, and use. A true "somatic cell genetics" or a genetic system of extranuclear inheritance may also stem from this cell "hybridization" phenomenon. I also want to mention the phenomenon of "metabolic cooperation" between mammalian cells in culture. This phenomenon, similar to "complementation" in microbes, and described by Subak-Sharpe, Burk and coworkers, involves the tranfer of an enzymic capacity from one cell type to another in mixed culture. Originally described for cells deficient in inosinic pyrophosphorylase (IPP) and HGPRT (Lesch-Nyhan syndrome) it has recently been extended to cells from individuals with the Hurler and Hunter syndromes by Fratantoni *et al.* The basis of this "metabolic cooperation" is not as yet certain, but it has the potential of leading to means of corrective treatment of these and other hereditary diseases.

In this all too limited time, I have tried to illustrate with a few examples the basic applicability and pertinence to child health of the concepts and techniques of molecular biology. In perspective, it seems clear that the techniques and concepts developed with simpler forms are indeed applicable to the human situation, since genes and molecules have essentially similar roles and interrelationships in all forms of life, from microbes to man. Experimentally, as well as theoretically, analysis of gene function in terms of a single gene difference is as applicable and as powerful an approach to the human situation as with microbes. Actually, in some ways man is a more versatile and promising organism and may have even more to contribute to our basic knowledge of molecules and genes. Problems in man can be studied at the cell level in culture, as well as in tissues and organs, and in the intact organism. The study of man's problems is facilitated and expanded by the use of genetically standardized experimental animals such as mice, in which models of human problems such as diabetes, anemia, muscular dystrophy, and inherited neurological and developmental diseases are becoming available in increasing numbers and varieties. Man offers other opportunities of inherent versatility and challenge, compared to microbes. The relationships of genes and molecules can be studied in an additional dimension, that of development and differentiation. Furthermore, in man the more complex organization of genetic material into chromosomes gives this added dimension to basic studies.

Another promising area concerns man's unique capacity for learning and reasoning. This area provides exciting challenges and possibilities of understanding mental processes in terms of molecules and genes, and of doing something about problems such as mental retardation.

In addition, and protestations by some basic scientists to the contrary, the study in man himself of basic biological problems brings with it the double satisfaction of adding to basic knowledge and at the same time contributing directly and effectively to man's health and well being. It seems to me that in the health field, the area concerned with our most precious resource, our children, is perhaps both the most challenging and the most rewarding.

Finally, for its many notable contributions to Child Health I want to congratulate The Children's Hospital Medical Center on this anniversary, and wish for it even greater success in meeting the challenges of the second century it is now beginning.

THE CRITICAL ROLE OF ULTRASTRUCTURE IN PEDIATRIC PATHOLOGY

Betty Geren Uzman, M.D.

Associate Professor of Pathology
The Children's Cancer Research Foundation

Shortly before the beginning of the century we celebrate today – and as part of his first lecture in the series, "Die Cellularpathologie," Virchow proclaimed: "The history of medicine teaches us . . . that every more important epoch has been directly ushered in by a series of important discoveries concerning the structure of the body . . . What Schwann, however, has done for histology has as yet been put in a very slight degree built up and developed for pathology, and it may be said that nothing has penetrated less deeply in the minds of all than the cell-theory in its intimate connection with pathology."

A century later, Linus Pauling was to discover the first "molecular disease" (of hemoglobin) and to cue – with his solution of protein structure, the alpha helix – a revolution called molecular biology. Recognition of DNA→RNA→Protein as life's central ordering and sequencing processes allowed the student of human development and disease to match prediction with prototype.

A host of amino-aciduria's would be discovered, since the amino-aciduria of Wilson's disease was already known; dysgammaglobulinemia's were bound to exist in the same world as agammaglobulinemia; and, if folic acid antagonists could interfere with tumor DNA synthesis, inhibitors of RNA and protein synthesis were sure to be cancerostatic. In short, "cellularpathologie" has yielded to "molekular pathologie"; and were Virchow here today he would have to say that nothing has penetrated more deeply in the minds of all than the molecular-theory in its intimate connection with pathology.

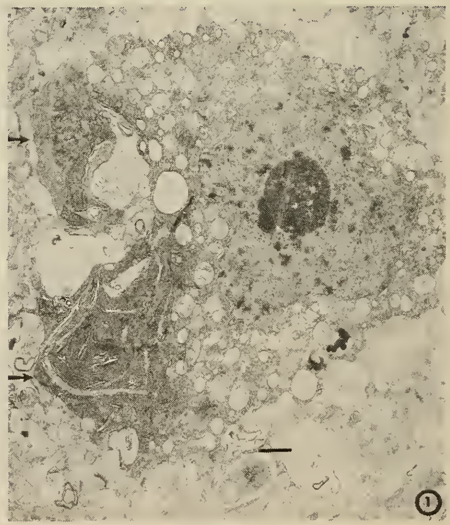

Figure 1

While the molecular biologists and geneticists may be said to have gone from molecules to dogma with x-ray diffraction and E. coli, the molecular pathologists rely heavily on the electron microscope and their rich heritage – a century of "protocols." The mysteries of pediatric pathology, in particular, have been subjected to one or another approach, and we should like to briefly review three situations in which the extended resolution of the electron microscope has critically influenced our understanding. The first case is one of three sisters, all affected – after apparently normal neonatal and early infantile development – with slowly progressive mental deterioration and loss of sensory and motor functions. This disease, infantile neuroaxonal dystrophy (IND), was described by Seitelberger, recognized in this family by Huttenlocher, and at autopsy had classic axonal spheroids in cord and brain stem. However, (Figure 1) examination of the cerebral cortex with the electron microscope revealed enormous masses of smooth membranes in positions ordinarily occupied by axo-somatic synapses. Dr. Nicholas Gonatas in Philadelphia had found, about three years earlier, similar but less advanced examples in axo-dendritic synapses of two children with mental retardation. Recently, the same lesions have been described in the brains of mice ill after injection with "scrapie" infected tissues. The accumulation of smooth membranes has been observed both in steroid secreting cells, and in hepatic cells following the administration of drugs that must be detoxified by hydroxylation in the liver. The ultrastructural lesions have been equated with bodies seen in Hematoxylin and Eosin sections of children with IND (Figure 2), bodies termed "corps eosinophiles" by Lyon and See. At once, the ultrastructural features suggest that a previously unrecognized cause of mental deterioration in healthy infants is *Synaptic Disease;* that it may be related to steroid metabolism or to obscure infection; and that attempts to isolate or grow a slow virus in such cases are not only indicated but justify cortical biopsy in a successively affected sibling to obtain viable material.

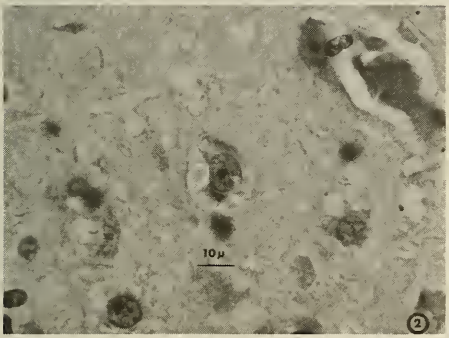

Figure 2

A second disease, *pneumocystis pneumonia,* has plagued the orphanages of northern Europe where it was originally recognized and ascribed, according to silver stains, to a "protozoan" termed *Pneumocystis carinii.* No one has been able to grow this organism in culture. A number of investigators have described both thick and thin-walled cysts in electron micrographs (Figure 3). In our three cases, the thin-walled cysts have suggested the possibility that they be viral-associated structures (Figure 4). Figure 5 illustrates, at higher magnification, their resemblance to well-recognized viral coat structures of myxoviruses. In our cases, the thick-walled cysts have not contained recognizably viable cell particulates. At present, this disease is more and more common in patients receiving a host of immunosuppressive drugs. The response of these patients to antibiotics against protozoal diseases together with the ultrastructural demonstration of well-preserved, thick-walled structures in a similar disease in rats (produced after prolonged, large doses of corticosteroids) supports

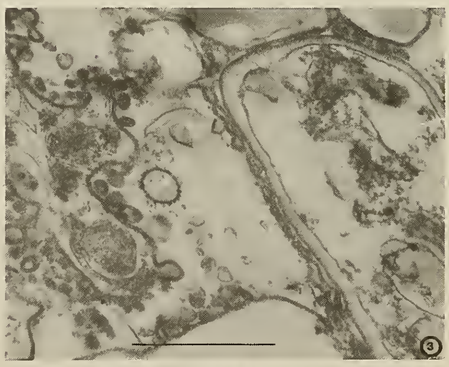

Figure 3

the theory of viable, unicellular, etiologic agents. On the other hand, Dr. Gordon Vawter has obtained sera from three patients, courtesy of Dr. Adam Nowoslawski of Warsaw, and when they were examined by Drs. John L. Sever and Wallace Rowe at the National Institutes of Health, two had elevated titers of antibodies to Respiratory Syncitial Virus. Thus, the ultrastructural approach is stimulating dual explorations for the etiologic agent, and it is to be hoped that this 50-year mystery will soon yield to these concerted attacks.

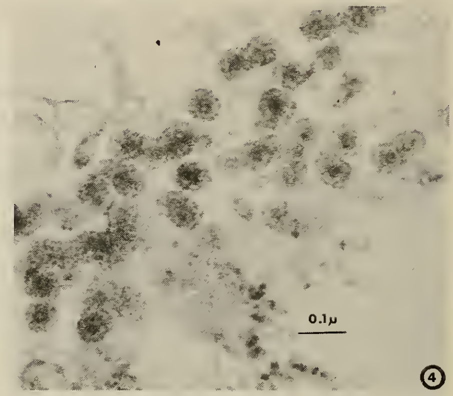

Figure 4

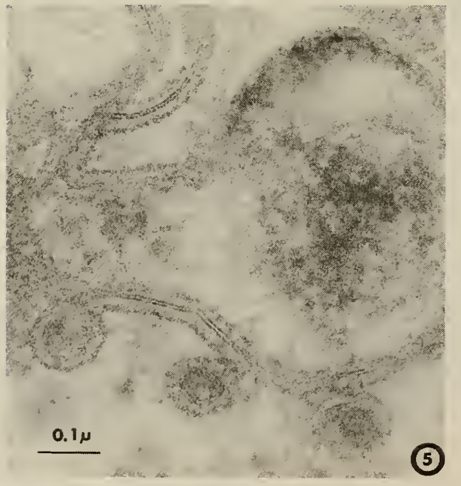

Figure 5

Finally, a brief description of our attempts to localize those long-lasting molecules that enter the white matter of the brain during myelination and remain until maturity. In his Blackfan lecture, Dr. Rene Dubos summarized years of research and described the effects on growth and learning of sub-optimal nutrition during the period of myelination and brain growth in mice. Dr. J. Dobbing, speaking last December at the International Pediatric Congress in Mexico City, reviewed his and other workers' extensive evidence that certain lipids remain in white matter (and sciatic nerves) from myelination until maturity; that others have shorter half lives; and that in a number of rodents and in pigs, the period of myelination (brain growth) is particularly vulnerable to nutritional inadequacies.

In our laboratories, the myelin sheath has been the focal point of ultrastructural studies of the developing nervous system and we set about to localize the long-lasting molecules of cholesterol in mouse sciatic nerve. In Figure 6, an autoradiograph, one can see silver grains (activated by the emission of low energy beta rays from cholesterol-1,2^{-3}H) present in the myelinating sciatic nerve three hours after it was injected intraperitoneally at 5 days of age. Figure 7 is an electron autoradiograph of the same nerve. In both slides, many grains were seen over myelin, but note that at the ultrastructural level, those not on myelin may be referred to activity in other tissue compartments. Statistical analyses of sciatic

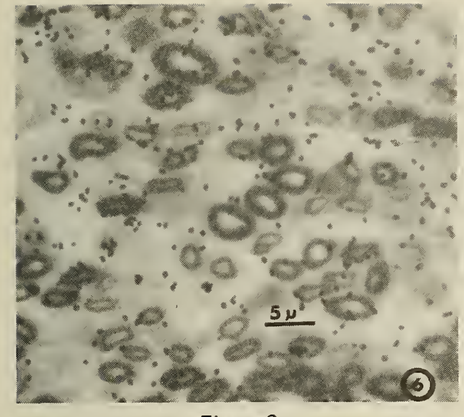

Figure 6

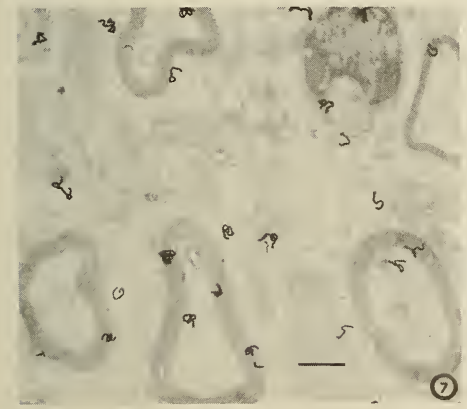

Figure 7

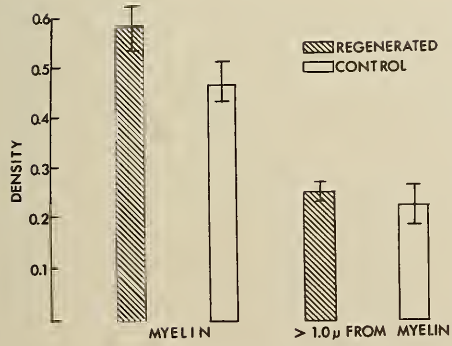

Figure 8

nerves obtained hours, days, or weeks after cholesterol-1,2^{-3}H injection at 5 or 8 days of age have been rigorously carried out, and it is quite clear indeed that at any time, cholesterol-1,2^{-3}H is found in some compartments other than myelin, such as the axoplasm, the Schwann cell, etc. If one removes part of such a mouse nerve that was labeled during myelination, and examines the segment regenerated during a period of a month, one can compare the distribution of label in a non-operated collateral with that in the newly formed segment (Figure 8). Once again, cholesterol-1,2^{-3}H is at highest density in the new myelin but is also present outside the myelin sheaths. We propose that the barrier to cholesterol loss from peripheral nerve is not the perineurium, is not perhaps even a specific blood-nerve-barrier, since cutting out a segment of nerve opens up the perineurium and breaks vascular channels, yet cholesterol-1,2^{-3}H not only remains, but achieves a high density in the new segment. The tentative conclusion is that cholesterol must be "bound" within the nerve or its individual fibers. The nature of this binding force or agent is unknown; but a myelinating nervous system in order to achieve optimal development must have, not only a supply of nutrients, but also a milieu appropriate for the metabolism of nutrients and for the selective binding of myelin constituents. The fact that "rats born of and suckled by malnourished mothers are similarly deficient in their learning capacity" brings us once again to the starting point, that is, to the method of propagation of acquired defects or, put another way, the influence of inadequate building blocks on the natural sequencing and programming controls of cellular potentials.

Drs. Floyd Gilles and Tessa Hedly-Whyte have carried out the studies of infantile neuroaxonal dystrophy; Dr. Gordon Vawter, Dr. Jules Edlow and Dr. David Liknaitsky have contributed to the investigations of pneumocystis pneumonia; and the collaborators on the studies of myelination have been Drs. Tessa Hedly-Whyte, Frank Rawlins, Miriam Salpeter (Cornell University) and Gloria Villegas (Instituto Venezolano de Investigaciones Cientificas). Dr. Sidney Farber has fostered all the work, particularly encouraging the ultrastructural approach to problems in pediatric pathology.

Supported by grants from the National Cancer Institute (C-6516; FR05526) of the National Institutes of Health; from the legacy of Loula D. Lasker; from the Albert and Mary Lasker Foundation, New York; from the National Institute of Neurological Diseases and Stroke (NB-00190); and from the National Multiple Sclerosis Society.

CEREBROSPINAL FLUID PHYSIOLOGY IN HEALTH AND DISEASE

Gordon V. Watters, M.D.

Associate in Neurology
The Children's Hospital Medical Center

The studies reported in this paper are the result of a combined project involving the Department of Neurology, under Charles F. Barlow, M.D. and the Department of Neurosurgery, under Donald D. Matson, M.D. Those directly involved in the studies include Doctors Robert W.P. Cutler, Joseph H. Galicich, Antonio V. Lorenzo, Larry K. Page, and Gordon V. Watters.

Although our understanding of many aspects of human cerebrospinal fluid physiology is still incomplete, there is a body of evidence which indicates that under normal conditions, the ventricular choroid plexuses are the site of cerebrospinal fluid formation. The fluid then flows out of the ventricles into the subarachnoid space, to be absorbed into the venous system via the arachnoid villi as a bulk flow phenomenon. The volume of cerebrospinal fluid formed in man and its rate of absorption have been the subject of considerable controversy. It is clear that knowledge of the normal rate of formation and absorption is essential if the pathophysiology of such common disorders as hydrocephalus is to be understood. A variety of techniques have been used to study spinal fluid dynamics and physiology, but an important advance was made when Pappenheimer and his group introduced a method of perfusion of the cerebrospinal fluid in 1962. (1)

Rubin and co-workers (2) were the first to use this technique in man, in the treatment of cerebral neoplasms. From these studies in adult patients, they have reported values for the rate of formation of cerebrospinal fluid and its relation to spinal fluid pressure. We are presenting data first from a group of children, age 4 through 13 years, who were perfused with chemotherapeutic agents by the venttriculolumbar route in the treatment of cerebral neoplasms and chronic encephalitis. (3) Thirty-two perfusions were performed in these children, all of whom had normal spinal fluid pathways. Data from these normal patients have provided a comparison for data obtained from perfusions performed in a second group of patients who had abnormal cerebrospinal fluid pathways as evidenced by a rapidly enlarging head, large ventricles, or chronically increased cerebrospinal pressure.

Artificial cerebrospinal fluid (Elliot's B solution) containing tracer quantities of RISA and the chemotherapeutic agent was introduced into the right lateral ventricle via a plastic cannula, an Ommaya device, and was collected from a needle in the lumbar subarachnoid space. With the patient in the left lateral position, the outflow pressure was monitored by a manometer with zero point at the level of the spinous processes. Adjustment of outflow pressure and hence, cerebrospinal fluid pressure was accomplished by raising or lowering the outflow tubing. The rate of perfusion varied from 1.45 to 1.90 ml/minute but after initial adjustment was constant to 3 to 5 percent in an individual study. Perfusion time varied from 2½ to 6 hours. Inflow and outflow rates were monitored by photoelectric drop counters and drop size was determined gravimetrically.

The data from a typical perfusion are presented in graphic form in Figure 1. Line V_i and V_o represent inflow and outflow rates respectively in ml/minute. The relative constancy of inflow and outflow is indicated by their level course across the graph.

Line C_o is the outflow concentration of RISA in CPM/ml plotted against total effluent in ml. The low level of radioactivity in the outflow at the beginning of the perfusion is shown at the left of the figure, while a steady state equilibrium is seen to occur after about 160 to 200 mls of fluid has been perfused. After achieving this steady state, the formation rate may be calculated from the dilution of the infused RISA, using the formula

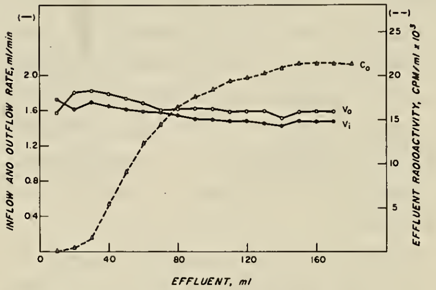

FIGURE 1: Data from a representation perfusion. Inflow (V_i) and outflow (V_o) rates and effluent RISA concentration (C_o) are plotted against cumulative effluent volume.

$$V_f = \frac{C_i - C_o}{C_o} \times V_i$$

where C_o = outflow concentration
C_i = inflow concentration
and V_i = rate of inflow in ml/min.

Once the rate of formation is known, the rate of absorption is calculated using the simple fluid balance in which absorption is equal to the difference between inflow and formation on the one hand, and outflow on the other. This relationship is expressed in the formula

$$V_a = V_i + V_f - V_o$$

where V_i = rate of inflow
V_f = rate of formation
and V_o = outflow rate in ml/min.

The volume of the cerebrospinal fluid compartment may be calculated measuring mathematically the area under the curve C_o. The formula used is

$$Vol_{csf} = \Sigma \left[\frac{V_i C_i - (V_o + V_a) C_o}{C_{ss}} \right] \Delta t + DS$$

where V is volume rate in ml/min, C is radioactivity in counts per minute/ml, subscripts i, o, and ss refer to inflow and steady-state respectively, n is the number of samples, Δt is the time interval per sample in minutes, and DS is the dead space of the outflow tubing in *ml.*

The rate of formation was determined on 21 occasions in 11 patients, all of whom had normal cerebrospinal fluid pressures. As seen in Figure 2, spinal fluid pressure over the range of 0 to 200 mm cerebrospinal fluid had no apparent effect on the rate of formation of cerebrospinal fluid, and the slope of the regression line of formation, as a function of pressure, did not differ significantly from zero. The mean rate of (C.S.F.) formation of cerebrospinal fluid was *0.35 ml/min* or about 500 ml per day.

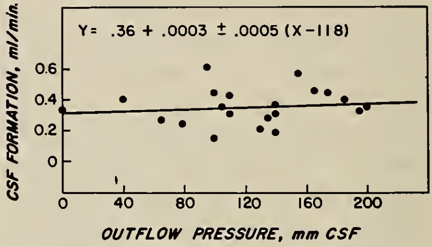

FIGURE 2: Relationship between outflow pressure (cerebrospinal fluid pressure) and cerebrospinal fluid formation rate over the pressure range 0 to 200 mm cerebrospinal fluid.

Since rate of formation had been seen to be unaffected by spinal fluid pressures over the range 0 to 200, it was possible during a single perfusion to alter the spinal fluid pressure at intervals by raising or lowering the outflow cannula and obtain values for rate of absorption at several different pressures during an individual study.

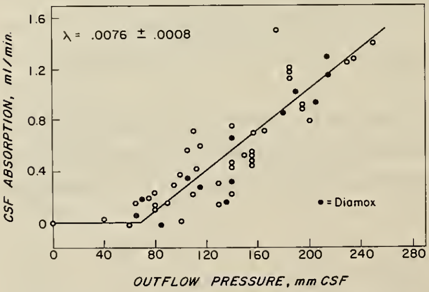

FIGURE 3: The relationship between cerebrospinal fluid absorption rate and outflow pressure. The open circles are from patients not receiving diamox and the slope is of the least squares regression for these values only.

Forty determinations of rate of absorption were made in 11 patients, at spinal fluid pressures ranging from 0 to 250. These values are plotted in Figure 3 with rate of cerebrospinal fluid absorption as the ordinate and cerebrospinal fluid pressures as the abscissa. It may be seen that the rate of absorption increased in a linear fashion with increasing pressure over the range 68 to 250, and perhaps even beyond this point. At a cerebrospinal fluid pressure of 68, the rate of absorption was zero and remained zero at pressures below this level. This value of 68 mm. cerebrospinal fluid, above which spinal fluid absorptions begin to occur and below which there is none, may well represent the mean opening pressure for the valves of the arachnoid villi.

A schematic abstraction of the relationship between rate of absorption, rate of formation, and spinal fluid pressure is presented in Figure 4. The two relationships already alluded to are noted. *First,* rate of formation is unaffected by spinal fluid pressures; *next,* rate of absorption is zero up to a pressure of 68, after which it increases in a linear fashion. It is noteworthy that rate of formation and rate of absorption are equal at a pressure of 112 mm cerebrospinal fluid. This value presumably represents the average physiologic pressure within the cerebrospinal fluid compartment in normal patients in a horizontal position.

Resistance to absorption of spinal fluid is also indicated on this graph by the slope of the line for absorption as a function of pressure. From this it may be seen that in man a major increase in rate of formation of two or threefold, say from 0.4 to 1.2 mm/min, would only increase the average spinal fluid pressure from 110 to 210 mm cerebrospinal fluid. This suggests that in man, increased rate of formation is not likely to be a significant factor in producing elevated cerebrospinal fluid pressure in conditions such as hydrocephalus.

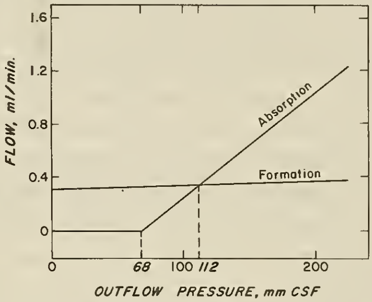

FIGURE 4: Regression lines for cerebrospinal fluid formation and absorption as a function of pressure. The intercept at 112 mm. indicates the pressure at which formation and absorption are equal. The pressure at which absorption is zero is also indicated.

The second group of patients included 8 children, age 9 months to 14 years, and 2 adults, all of whom had abnormal cerebrospinal fluid pathways. The mean rate of cerebrospinal fluid formation for this group was 0.33 ± 0.03 ml/min, not significantly different from the normal 0.35 ± 0.02 ml/min. Short term alterations of pressure in these patients over the range 45 to 355 mm had no apparent effect on the rate of cerebrospinal fluid formation. The slope of the regression of rate of formation as a function of outflow pressure did not differ from zero $Y = 0.332 + 0.002\,(x - 179.9)$. Thus it appeared that rate of cerebrospinal fluid formation was independent of short and long term alterations of intracranial pressure in these patients with abnormal cerebrospinal fluid pathways and was similar to normals.

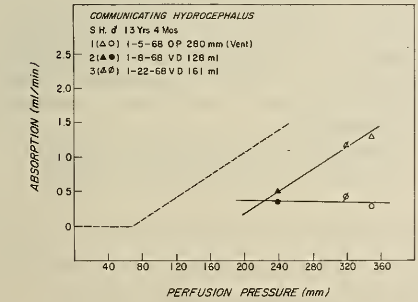

FIGURE 5: Type 1: Abnormal relationship between cerebrospinal fluid absorption and pressure in a patient with communicating hydrocephalus (solid line) compared with absorption pressure relationship in normals (interrupted line).

△ indicates rate of absorption in ml/min
0 indicates rate of formation in ml/min

In contrast, cerebrospinal fluid absorption was markedly different in the patients with hydrocephalus. In some, the rate of absorption was 0.0076 ± 0.002 ml/min/mm the same as in normals, but this pressure-absorption relationship did not begin until pressures considerably higher than 68 mm were established. Figure 5 shows the data for one such patient. The normal pressure-absorption relationship is indicated as an interrupted line. The rate of formation in this patient, indicated by the line joining the circles, is in the normal range and is independent of pressure, while the absorption pressure relationship indicated by the line joining the triangles is shifted to the right, to the extent of about 100 mm. The slope of this line, however, remains the same as in normals. Thus, such patients appeared to require a higher opening pressure before cerebrospinal fluid absorption began to occur. Thereafter, absorption increased at a normal rate with each increment in pressure. However at any given pressure above 68 mm, cerebrospinal fluid absorption remained markedly less than in normals.

In other hydrocephalic patients absorption began to occur at approximately the same pressure as in normals, but thereafter increased at 0.0040 ± 0.0004 ml/min/mm, a rate much more slower than normal. The data from one such patient is shown in Figure 6. Again cerebrospinal fluid formation, indicated by the line joining the circles is in the normal range. Absorption in this instance is seen to begin in the normal range, but the line joining the triangles, relating absorption and pressure, has a more gradual slope than normal. Thus, in these patients there appeared to be a uniformly increased resistance to absorption of cerebrospinal fluid over a considerable pressure range.

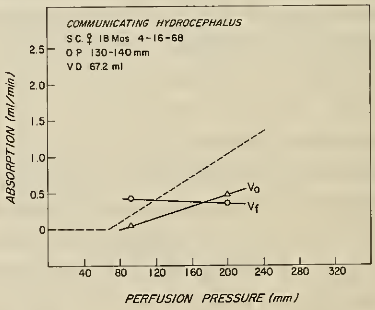

FIGURE 6: Type 2: Abnormal relationship between cerebrospinal fluid absorption and pressure in a patient with communicating hydrocephalus (solid line) compared with absorption pressure relationship in normals (interrupted line).

△ indicates rate of absorption in ml/min

0 indicates rate of formation in ml/min

These quantitative studies of cerebrospinal fluid circulation in patients with abnormal cerebrospinal fluid pathways support the widely held hypothesis that increased resistance to cerebrospinal fluid absorption is a major factor in the pathogenesis of hydrocephalus. These studies also suggest that there are at least two different mechanisms involved in the pathophysiology of the absorptive defect.

In summary, it has been found that in normal children and in patients with hydrocephalus the rate of formation of cerebrospinal fluid was 0.35 ml/min or 500 ml/day. The rate of cerebrospinal fluid formation appeared to be independent of short or long term changes in cerebrospinal fluid pressure.

In the normals, rate of absorption increased with pressure in a linear fashion over the range 68 to at least 250 mm cerebrospinal fluid. At pressures below 68, rate of absorption was zero, suggesting that this pressure was the pressure required to open the absorptive channels connecting spinal fluid and blood. At a pressure of 112 mm, rate of absorption was equal to rate of formation, which presumably represents the resting physiologic pressure in the left lateral position. In the patients with abnormal cerebrospinal fluid pathways, the normal relationship between rate of cerebrospinal fluid absorption and pressure was altered. At least two pathophysiological abnormalities of absorption were indicated which may relate to the pathogenesis of hydrocephalus.

REFERENCES

1) Pappenheimer, J.R., Heisey, S.R., Jordon E.F., and Downer, J.D., Perfusion of the cerebral ventricular system in unanesthetized goats, *Am. J. Physiol.* **203**: 763-774, 1962.

2) Rubin, R.C., Ommaya, A.K., Henderson, E.S., Bering, E.A. and Rall, D.P., Cerebrospinal fluid perfusion therapy for the treatment of central nervous system neoplasms, *Neurology* **16**: 680-692, 1966.

3) Cutler, R.W.P., Page, L.K., Galicich, J., and Watters, G.V., Formation and absorption of cerebrospinal fluid in man, *Brain* **91**: 707-720, 1968.

HEREDITARY ANGIONEUROTIC EDIMA:

ETIOLOGY, PATHOGENESIS AND THERAPY

Fred S. Rosen, M.D.

Chief, Immunology Division
The Children's Hospital Medical Center

The past twenty years has witnessed a remarkable Renaissance in medicine, through the study of hereditary disease. It staggers human comprehension to reflect that only thirty-five years of our century elapsed, less than the life span of most people in this room, between the serious hemorrhages of the Tsarevich at Biolowieza and at Spala in the summer of 1912 to the demonstration of a molecular difference between normal and sickle cell hemoglobin by Pauling; thirty-five years from the time when that most royal family, with all the wealth and power in the world at its command, knew neither the cause nor the cure, nor even the fact that the princeling's ailment was in fact hereditary to the foreshadowing of the simple demonstration that a glutamic acid for valine substitution in hemoglobin caused sickling of red cells. I wish, in this brief moment, to examine one of these human genetic models, the rarity of which, like all the rest, is rendered unimportant by the light which the pathophysiology of the defect sheds on normal homeostasis.

Hereditary angioneurotic edema is a disease which is characterized by recurrent episodes of painless, non-tender, non-puritic swelling. In addition to these periodic episodes of edema, vomiting or diarrhea occurs when the gastrointestinal tract is involved. Death from laryngeal edema shortens the life on one-third of affected individuals. The episodes of edema are self-limited and last 48 to 72 hours.

The disease occurs in individuals who have an hereditary deficiency of the inhibitor of C1 esterase. This α_2 glycoprotein inhibits the action of activated first component of complememt on its natural substrates, C2 and C4, and on certain synthetic esters, primarily N-acetyl tyrosine ethyl ester. Examination of a large number of kindreds illustrates that the defect is transmitted as a Mendelian autosomal dominant so that affected individuals are in fact heterozygous for the trait. However, in 85% of affected kindreds, only 17.5% of the normal level of C1 esterase inhibitor is present. In the remaining 15% of the kindreds an abnormal gene product which does not function biologically is present in normal immunochemical amounts. In fact, each of these families with immunochemically detectable but biologically inert inhibitor has its own uniquely abnormal gene product which can be demonstrated by the immune fixation technique.

Now we must turn to the question of the mechanism of the edema formation in affected persons. C1 esterase activity is generated in plasma *in vivo* during attacks of angioedema. No such activity is ever demonstrable in normal plasma. It can in fact be shown that C2 and C4, though substrated of C1 esterase, are consumed during attacks of angioedema. Purified C1 esterase injected into normal persons produces localized angioedema; after an intravenous injection of Evans-blue vascular leakage at the injection site is evident and can also be reproduced in guinea pigs. The post-capillary venules of carbon injected guinea pigs spring a severe leak after injection of this material. We were furthermore able to induce attacks of angioedema with the purified C1 esterase in patients with hereditary angioneurotic edema. However, we found that individuals genetically deficient in C2 were unresponsive to the material. It thus appeared to us that a vasoactive peptide may be split off C2. We have been able (1) to isolate a hitherto undescribed peptide from the plasma of patients with angioneurotic edema and (2) to generate a vasoactive peptide from mixtures of highly purified C1,4, and 2.

I have begged off answering the question of how the C1 activates to start an attack of angioedema. Many mediators may activate C1 and furthermore the inhibitor can block several of these steps. But herein lie the therapeutic possibilities because we have available now inhibitors, such as tranexamic acid, which appears to block these potential activation mechanisms.

In conclusion, we must agree with Quincke's original observation in 1882 that "der Vorgang dann der eigentlicken Entzündung näher verwandt erscheint" and hope that we have vitiated Sir William Osler's plea of 1888 that "we have to do here with clinical facts and observations which urgently call for scientific solution for we possess at present but extremely scanty material for an adequate explanation regarding the neurotic edema."

This talk has resulted entirely from the patient diligence and insights of my colleagues Dr. Virginia Donaldson and Dr. Martin Klemperer and the willing cooperation of many patients afflicted with the neurotic edema.

THE CHOREIFORM MOVEMENTS AND BEHAVIOR DISTURBANCES

Peter H. Wolff, M.D.

Associate in Psychiatry,
The Children's Hospital Medical Center

The choreiform syndrome, originally described by Prechtl and Stemmer is characterized by choreiform movements, or slight motor jerks of brief duration that occur irregularly and arrhythmically in different muscles (1). These movements were found to occur more frequently in children exhibiting behavior disorders like hyperkinesis, defects of concentration, and learning difficulties; and in prospective and retrospective studies, they were found to correlate with a history of perinatal distress (2, 3).

In a previous publication, we reported the incidence of choreiform movements in a group of normal 10-14 year old children from a suburban school system, in a similar group of Japanese children, and in various populations of emotionally distrubed children and adolescents (4). Ten per cent of normal children, and from 32-68% of children from deviant populations were found to have abnormal movements; in all groups that included boys and girls, the incidence was 2-3 times greater among the boys.

A number of recent publications have reported a significant association between *major* neurological disorders and *gross* psychiatric disturbances in children (5, 6). There is, however, no consensus about the clinical implications of minor neurological signs for less severe behavior disorders or learning disabilities. In fact the concept of minor cerebral dysfunction as a distinct entity has been questioned by various authors (7, 8, 9, 10).

Stemmer (11) and Rutter *et al* (12), for instance, found no correlation between choreiform movements and behavior disturbances, whereas our initial study indicated that choreiform movements are associated with various psychiatric disorders. Contradictory findings have also been reported about the clinical significance of other 'soft' neurological signs (13). Since the realm of minor cerebral dysfunction despite its vague boundaries, its questionable etiology, and the difficulty in making a diagnosis, presents a major diagnostic and therapeutic problem to the pediatrician and child psychiatrist, we thought that a further investigation was warranted to clarify the contradictory reports about the clinical implications of one such entity – namely, choreiform movements.

Our earlier cross-sectional study was therefore extended, and the behavioral implications of choreiform movements were determined in two separate steps: (A) In a relatively homogeneous population of *normal* school children, the incidence of choreiform movement was correlated with the teachers' reports about overall school performance, academic achievement, and behavioral characteristics in the classroom. The independence of judgments was guaranteed by the fact that we did not know the teachers' reports before making our assessments, while the teachers were not aware of the study or its results. (B) In a population of juvenile delinquent boys and girls being held at a detention center, the incidence of choreiform movements was correlated with performance on a simple psycho-technical task of rhythmical tapping.

By these two approaches we hoped to determine whether choreiform movements are correlated with variations in the adaption of normal children to school activities; and whether choreiform movements in a known deviant population are correlated with competence in a sensory motor task which we assume to pertain to serial organization in behavior (14).

A. *Choreiform Movements and School Performance*

1. Procedure: In the school system from which our original sample of normal school children was drawn, the teachers make yearly reports about the children's general academic performance and specific abilities in reading, spelling, arithmetic, and other learning skills. They also describe the children's behavior in the classroom with emphasis on motivation, attention span, peer relations, cooperation, and the like; and they indicate whether a child has been referred and accepted for psychiatric treatment, remedial teaching, or other special services.

From a preliminary survey of the school records we prepared a check list of 18 items that occurred frequently in the teachers' reports (see Table 1). Since the teachers did not write their reports according to a standard vacabulary, it was necessary to prepare a "dictionary" of synonyms in order to translate the teachers' language into the corresponding categories of our protocol. "Works hard", "is conscientious", and "does not exert much effort," for instance, were tabulated under motivation, while references to concentration or distractibility were scored under attention span. The dictionary was complete enough so that all but a few comments could be entered in the check list, and there was no need to interpret what the teacher might have meant. When two investigators assessed all the school records independently, inter-observer reliability for all items ranged from 84-100%. For items which were subsequently found to be significantly correlated with choreiform movements, inter-observer reliability ranged from 93-100%.

The teachers reported an item only when the behavior in question differed notably from the group average in the positive or the negative direction. In other words, they did not rate every child on every item included in our protocol. The analysis of individual items is therefore based on only those cases mentioned by the teacher as being out of the ordinary for the item in question. Non-parametric statistical procedures were used throughout (15).

2. The Sample: The experimental populations consisted of 103 boys and 25 girls from the original sample of 1300 normal school children, who had unequivocally demonstrated choreiform movements. The control group consisted of 103 boys and 25 girls without choreiform movements selected from the same sample and matched for age and social class. In the three-year interval between the original incidence study and the review of records for the present study, some of the school records had been lost, most often because the children had moved. The records for 95 of the 103 boys with choreiform movements, for 75 of the 103 boys without choreiform movements, and for all 50 girls with and without choreiform movements could be traced. These constituted the final sample. Raw scores for boys were corrected to compensate for differences in sample sizes.

3. Results: *Boys:* Choreiform movements were independent of social class membership, as rated by father's occupational classification on the Hollingshead-Redlich Scale (16). Differences in I.Q. scores and general academic achievement for the two groups of boys did not reach statistical significance (see Tables II, III). Performance in specific academic skills also did not differ in the two groups, with the exception that boys without choreiform movements (CM- boys) had fewer reading difficulties than boys with choreiform movements (CM+ boys), ($p<.05$); and more of the CM+ boys had difficulties in spelling ($p<.01$; see Table IV).

Choreiform movements were strongly associated with a number of behavioral disturbances. We had assumed from the start that the relation between soft neurological signs and behavior disorders would vary with the individual life histories of particular children, and we would probably find no well delineated syndrome composed of one neurological sign and a specific set of disturbances in behavior. For an initial assessment we therefore grouped all 12 items of the protocol pertaining to behavior in the classroom rather than to academic performance as a cumulative behavioral rating (see Table I). A child was scored as having a favorable or unfavorable rating if at least two-thirds of the behavior items mentioned by the teacher pointed in one direction. When the teacher made mention of only one behavioral characteristic for a child, this was also counted as a corresponding score. According to the cumulative behavior ratings, the CM+ boys received significantly fewer favorable reports than CM- boys ($p<.001$); and significantly more unfavorable reports than CM- boys ($p<.001$; see Table V).

On particular behavior items, CM+ boys were less well motivated ($p<.001$); more immature; ($p<.05$); had poorer working habits ($p<.001$); cooperated less with teachers and classmates ($p<.01$); were less well coordinated in their movements ($p<.001$); and had more frequent speech and hearing difficulties ($p<.01$; see Table VI). Differences in the incidence of psychoneurological disturbances in the two groups, as reported by the teachers, did not reach statistical significance. More of the CM+ boys, however, had been referred for psychiatric treatment or remedial teaching, and been accepted for these special services ($p<.025$).

In a normal school population, choreiform movements among boys were for the most part independent of academic achievement and I.Q. scores, except for a suggestive association with reading and spelling difficulties than CM+ boys. A significant association was found, however, between choreiform movement and various behavior disturbances that might influence attitudes toward school work, social relationships in the classroom, and neuropsychological competence.

Girls: Choreiform movements were also independent of social class membership for girls, again rated by father's occupational classification on the Hollingshead Redlich Scale. Differences of I.Q. scores in the two groups were statistically significant, with an 11.5 point difference in mean scores ($p<001$; see Table II). Of greater interest than the difference in I.Q. scores, was the *direction* of the difference. The I.Q. scores of CM+ girls were generally *higher* than those of CM+ girls, whereas we would have predicted an inverse correlation. Although differences in general and specific academic achievement between CM- and CM+ girls did not reach statistical significance, more CM+ girls than CM- girls had records indicating good general academic performance (see Table III, VII).

On the cumulative behavior ratings, CM- girls recieved more favorable reports and CM+ girls more unfavorable reports ($p<.025$; see Table VIII). Despite their higher I.Q.'s the CM+ girls, like CM+ boys, were *less* well adapted in behavioral terms to the classroom than CM- girls. On particular behavior items, girls without choreiform movement were reported to be more mature ($p<.01$), and more cooperative ($p<.01$; see Table IX). Although the sample of girls in this study was smaller, there was a distinct dissociation between the academic potential (as measured by I.Q. scores) and classroom behavior of girls with choreiform movements.

B. *The Relation of Choreiform Movements and Voluntary Motor Rhythms*

1. Method: A second step in our assessment was to correlate choreiform movements with performance on a sensory motor task that was designed to measure the subject's competence in voluntary motor rhythms. The subjects were instructed to tap at a rate which was "comfortable" for them, while keeping the pulses or beats as regular as possible throughout the performance. They were told to tap on two telegraph keys (one for each hand), first with both hands simultaneously (condition a); and then with the left and right hands alternately (condition b). In a third task (condition c) subjects were instructed to tap as fast as possible with their dominant hand. Each trial lasted for one minute and the performance was recorded by an event marker on a paper chart mover. Records were visually analyzed for *mean rate* per minute for each hand.

2. Results: *Boys*: On the day before the tapping test, one of us (I.H.) selected the first 14 CM+ boys and the first 14 CM- boys from a group of male juvenile delinquents who were being held for adjudication at a detention center. After the boys were examined for choreiform movements, the names of the entire group were arranged in random order, and on the following day the boys were tested by the other investigator (P.H.W.) on the three tapping tasks outlined above. When the records were analyzed for mean *rate* per minute for each hand, and the results arranged in rank order and correlated with the presence or absence of choreiform movements, there was a strong *inverse* association between mean tapping rate and choreiform movements for condition (a) ($p<.001$); see Table X). All except one of the CM- boys tapped faster than all CM+ boys. Approximately the same inverse assocition was found to hold for condition (b), i.e., while the subjects tapped alternately with the left and right hands ($p<.001$). Inter-correlations between conditions (a) and (b) were statistically significant ($r_s = .84$; $p<.001$) (by Spearman rank correlation), but maximum tapping rates with the dominant hand were independent of choreiform movements and other tapping tasks.

Girls: Twenty-eight adolescent delinquent girls from a similar detention center were matched for age with the male delinquents. In this group choreiform movements were tested 10 minutes *after* the tapping test; to assure independence of judgment they were tested by an individual who had not administered the tapping test. 10 of the 28 delinquent girls (36%) were found to have choreiform movements, which is about the same incidence rate as that found in two populations of male delinquents of the same age (4).

When the tapping records were analyzed for rate, there was a significant association between choreiform movements and tapping rates for conditions (a) and (b), ($p<.05$); choreiform movements were independent of tapping rates in condition (c). Intercorrelations between rates for conditions (a) and (b) were statistically significant ($r_s = .87$; $p<.001$ by Spearman rank correlation). In contrast to delinquent boys delinquent girls *with* choreiform movements tapped faster than girls without choreiform movements. In other words, girls who were assumed to show evidence of minor neurological disturbances tapped faster than girls without such evidence.

The relatively high intercorrelation of tapping rates for conditions (a) and (b) in boys and girls, suggests that we were testing a general sensory-motor skill, different in kind from that required for tapping at a maximum rate.

DISCUSSION

Our findings do not justify a lengthy and probably fruitless, discussion about the significance of the choreiform *syndrome* or about minor cerebral dysfunction as a distinct clinical entity. The study was undertaken on the assumption that somewhere in the mass of contradictory reports concerning the clinical significance of minor neurological disturbances there is buried a set of clinically valid facts. While these facts may not constitute a well defined syndrome, they can also not be dismissed as trivial since they reflect an important public health problem for pediatrics, child psychiatry, and perhaps also for obstetrics. We proceeded on the further assumption that it would be impossible to determine the size of the problem, or to plan for rational programs of prevention and early therapeutic intervention, until the various disturbances now globally classified as minor cerebral dysfunction have been isolated and their functional boundaries established.

Choreiform movements were chosen as a prototype of "soft" neurological signs because they are well defined and can be tested quickly and easily. In our experience interobserver reliability in making the test is also high when the sign is prominent. The demonstration by Prechtl and his associates that choreiform movements are correlated with a history and sub-clinical neurological signs of perinatal distress as well as with behavioral disturbances in later childhood, furthermore suggests possible preventive obstetrical measures or subsequent psychological interventions to prevent the minor neurological instabilities of the infant and their social consequences from becoming an important focus of conflict between parents and child (4). By labeling choreiform movements as a "prototype" of 'soft' neurological signs, we did not mean to imply that any clinical correlations found to be valid for the choreiform movements could be generalized to other neurological signs without independent empirical investigation.

The finding that in boys choreiform movements are associated with difficulties in reading and spelling was in agreement with Prechtl's original observations, but contradicts Stemmer's follow-up study and Rutter's cross-sectional findings (1, 3, 11, 12, 17). The significant associations in our study were not with academic performance or gross psychiatric illness, but with mild or moderate behavior disorders which in this study were found for both girls and boys, but for the most part did not interfere with the children's academic work.

A recent study conducted independently by Dr. Makkay and her associates on a segment of the same population of children examined in our study, has attempted to identify children who might subsequently become juvenile delinquents (18). In that study the teachers were asked to identify boys with significant behavior disturbances or signs of pre-delinquent behavior. From the initial survey of 1300 boys, Dr. Makkay and her associates selected a sample of 220 children with the most severe pathology, from which the final group was drawn for detailed study. 110 names on the list of 220 also appeared on the list of children we had tested, and 58% of the common sample were identified by us as having choreiform movements. The two studies were carried out independently on segments of the same population, and we interpreted these results as further supportive evidence that choreiform movements and behavior disturbances are significantly related, at least in boys.

One possible reason for the lack of agreement between our findings and those reported by Rutter et al (12), may be that we studied children from 10-14 years, whereas Rutter's group had studied children from 8-11. Like other 'soft' neurological signs, choreiform movements decrease in frequency with age, and can usually not be demonstrated in adults (19), even in chronic psychiatric patients residing in a mental hospital (20). By selecting the experimental subjects from an older group of children we may unintentionally have selected individuals in whom choreiform movements were most prominent.

Another possible reason for the conflicting results is that our comparisons were made *within* a population of presumably normal school children from a well-to-do and psychologically advanced school system, whereas many studies assessing the clinical significance of 'soft' neurological signs are either limited to psychiatrically deviant populations, or else compare normal and deviant populations. The same behavior disturbances which in our sample were not associated with academic deficiency might, under less favorable economic circumstances, be a causal factor in poor school adjustment and inadequate academic performance, even when the behavior disturbances are not severe enough to qualify as psychiatric illness. Thus

Hurwitz has found that 65% of a group of 100 adjudicated juvenile delinquent boys from lower social class familes and enrolled in over-crowded schools had been identified by their teachers as exhibiting severe learning problems (Unpublished Findings). The clinical significance of choreiform movements and other soft neurological signs can therefore not be determined without taking into account the child's social environment and its interaction with his particular behavioral disturbance (21).

Performance on the tapping test was selected as a measure of sensory motor competence on the assumption that rhythmical motor performance is a simple instance of a more general ability in the temporal organization of behavior (22), and that competence in this sphere of action may be a prerequisite for more complex sensory motor adaptations and symbolic thought (14). At present we are using a more refined version of the tapping tests in order to compare children's capacity for maintaining stable rhythms with their cognitive abilities.

Although the neurophysiological significance and neuroanatomical mechanisms involved in the various tapping tests are at present unknown, various tests of motor rhythm have been used in the neuropsychological and developmental assessment of children and adults. By comparing maximum tapping rates in the right and left hands, for instance, the Halstead neuropsychological battery looks for evidence of lateralization in cortical function (23). Two sub-tests of the Lincoln-Ozeretsky battery of motor development are specifically concerned with tapping, and many other of its sub-tests depend on competence in rhythmical motor performance (24). Stevens has reported that children with minimal brain dysfunction tap at a consistently slower rate than normal school children (25).

Since our limited goal was to explore the relation between two superficially independent aspects of motor behavior (the choreiform movement and tapping performance), it was not essential, although it would have been desirable, to know the neurophysiological basis for competence in rhythmical tapping. Our results indicate that boys with choreiform movements are deficient in a sensory motor function which we assume to be fundamental for the serial organization of behavior. The reason for this association was not clarified by the study.

The apparently paradoxical associations between choreiform movements and tapping rates among *delinquent* girls, and between choreiform movements and I.Q. scores in *normal* girls raises questions about the role of sex differences in neurological functions, psychological performance, and sensory motor competence, for which this study did not provide satisfactory answers. Psychological studies that give positive results when tested on male subjects, frequently give contradictory results when replicated on females. Perhaps for this reason many psychological studies are limited to the well known "young male adult college student" population, although such a device does not clarify the problem of sex differences. Male infants are generally more vulnerable to perinatal distress than females; and the behavior disturbances associated with presumptive signs of minor cerebral dysfunction are usually found twice or three times as often in boys as in girls (19). It is surprising, therefore, that all but a few studies concerned with the clinical significance of minor neurological signs either confine themselves to male populations, do not distinguish between the sexes in their reporting, or fail to include a large enough sample of females to make the results meaningful. Our various results suggest that the reported sex differences are not due simply to a greater incidence of minor neurological instabilities in boys, but that choreiform movements, and by extrapolation other soft neurological signs, may have *qualitatively* different implications for the social and intellectual adaptation of girls and boys. Any association between soft neurological signs and academic, behavioral or sensory motor disturbances found to be valid for boys, therefore cannot be generalized to the population at large until it has been tested with equal care in girls.

SUMMARY

The clinical significance of choreiform movements for academic performance, sensory motor competence, and behavior disturbances in children was tested by two methods: The incidence of choreiform movements in normal school children was correlated with the teachers' reports about the children's academic performance and non-scholastic behavior in the classroom. The preferred tapping rates of juvenile delinquent boys and girls were correlated with the presence or absence of choreiform movements.

In normal school children, academic performance was independent of choreiform movements except that 'choreiform positive' boys had greater difficulties in reading and spelling, whereas 'choreiform positive' girls had higher I.Q. scores. Boys and girls from a normal school population with choreiform movements exhibited a greater number of behavior disturbances than children without choreiform movements. Delinquent boys with choreiform movements were found to tap consistently slower than other male delinquents, whereas girls with choreiform movements tapped faster than delinquent girls without this sign.

It was concluded that choreiform movements do have a clinical significance particularly for behavioral disturbances not directly involved in academic performance, and for some sensory motor functions. No satisfactory explanations for the reported sex differences were offered, but is was concluded that this 'soft' sign of neurological disturbance has qualitatively different implications for behavior disturbance when it is found in boys and girls.

BIBLIOGRAPHY

1. Prechtl, H.F.R., and Stemmer, C.J. The choreiform syndrome in children. *Develop. Med. Child Neurol.* **4**: 119, 1962.
2. Prechtl, H.F.R. Neurological sequelae of prenatal and perinatal complications. *Brit. Med. J.* **4**: 763, 1967.
3. Prechtl, H.F.R. Reading difficulties as a neurologic problem in children. In *Reading Disbility: Progress and Research Needs in Dyslexia.* J. Money (Ed.), Baltimore: Johns Hopkins Press, 1962.
4. Wolff, P.H., and Hurwitz, I. The choreiform syndrome. *Develop. Med. Child Neurol.* **8**: 160, 1966.
5. Hertzig, Margaret, and Birch, H.G. Neurologic organization in psychiatrically disturbed adolescents. *Arch. Gen. Psyciat.* **19**: 528, 1968.
6. Graham, P., and Rutter, M. Organic brain dysfunction and child psychiatric disorder. *Brit. Med. J.* **3**: 695, 1968.
7. Schulman, J.L., Kaspar, J.C., and Throne, Frances M. *Brain Damage and Behavior.* Springfield, Ill.: Thomas, 1965.
8. Pond, D. Is there a syndrome of brain damage in children? *Cereb. Palsy Bull.* **2**: 296, 1960.
9. Werry, J.S. Studies on the hyperactive child. *Arch. Gen. Psychiat.* **19**: 9, 1968.
10. Pincus, J.H., and Glaser G.H. The syndrome of "minimal brain damage". *N.E. J. Med.* **275**: 27, 1966.
11. Stemmer, C.J. Choreatiforme bewegingsonrust. University of Groningen, Doctoral thesis, 1964.
12. Rutter, M., Graham, P., and Birch, H.G. Interrelations between the choreiform syndrome, reading disability and psychiatric disorders in children of 8-11 years. *Develop. Med. Child Neurol.* **8**: 149, 1966.
13. Bax, M.O.C., and MacKeith, R.C. (Eds.) *Minimal Cerebral Dysfunction.* London: Spastics Society, Heinemann, 1963.
14. Lashley, K. The problem of serial order in behavior. In Beach, F.A., Hebb, D.O., Morgan, C.T., and Nissen, H.W., (Eds.), *The Neuropsychology of Lashley,* New York: McGraw-Hill Book Co., 1951.
15. Siegel, S. *Non-parametric Statistics.* New York: McGraw-Hill, 1956.
16. Hollingshead, A.B., and Redlich, F.C. *Social Class and Mental Health.* New York: Wiley, 1958.
17. Prechtl, H.F.R. Prognostic value of neurological signs in the newborn infant. *Proc. Roy. Soc. Med.* **58**: 3, 1965.
18. Makkay, Elizabeth. *Newton-Baker Project Case Book.* Boston: Tru-print Lithographers, 1969.
19. Laufer, M.W., and Denhoff E. Hyperkinetic behavior syndrome in children. *J. Pediat.* **50**: 436, 1957.
20. Hurwitz, I., and Wolff, P.H. Unpublished findings, 1966.

21 Michell, G. Notes on the so-called 'minimal brain damage' syndrome with particular reference to family dynamics. In *Minimal Cerebral Dysfunction.* M.O.C. Bax and R.C. MacKeith (Eds.) London: Spastics Society, Heinemann, 1963.

22. Wolff, P.H. The role of biological rhythm in psychological development. *Bull. Menninger Clin.* **31**: 197, 1967.

23. Halstead, W.C. *Brain and Intelligence.* Chicago: University of Chicago Press, 1947.

24. Sloan, W. The Lincoln-Oseretzky test of motor development. *Genet. Psychol. Monog.* **51**: 183, 1955.

25. Stevens, D.A., Boydstun, J.A., Dykman, R.A., Peters, J.E., and Sinton, D.W. Presumed minimal brain dysfunction in children. *Arch. Gen. Psychiat.* **16**: 281, 1967.

TABLE I

ITEMS SCORED FROM TEACHERS' COMMENTS

	Item	Method of Scoring	
		present or absent	poor or good
ACADEMIC	General academic achievement		x
	Reading		x
	Mathematics		x
	Language		x
	Spelling		x
	Writing		x
BEHAVIORAL	Motivation		x
	Attention span		x
	Maturity		x
	Work habits		x
	Procrastination	x	
	Cooperation	x	
	Psycho-neurological problem	x	
	Underachievement	x	
	Hyperactivity	x	
	Peer relationships		x
	Coordination		x
	Speech-hearing problem	x	

TABLE II

I.Q. SCORES

	Mean	Range	t value
Boys			
CM+	114.9	81-159	.16 #
CM-	113.2	80-141	
Girls			
CM+	116.7	93-152	10.4 ****
CM-	105.2	81-130	

not significant
**** $p < .001$

TABLE III

GENERAL ACADEMIC ACHIEVEMENT

	Good	Average	Poor	x^2
Boys				
CM+	29	44	15	.61 #
CM-	25	26	9	
Girls				
CM+	13	8	2	1.4 #
CM-	8	11	3	

not significant

TABLE IV

SPECIFIC ACADEMIC RATING – BOYS

(Corrected scores)

Subject		CM+	CM-	
Reading	good	0	3	4.4 * (by Chi ^{2} Test)
	poor	16	9	
Mathematics	good	1	3	☐
	poor	5	4	
Language	good	1	1	☐
	poor	8	5	
Spelling	good	0	0	*** (by Binomial Test)
	poor	10	2	
Writing	good	3	0	☐
	poor	0	3	

*** $p < .01$

* $p < .05$

☐ sample not large enough to make results meaningful

TABLE V

CUMULATIVE BEHAVIORAL RATINGS – BOYS

(corrected scores)

Boys	CM+	CM-	x^2
Favorable reports	5	31	
versus			27.2 ****
Unfavorable reports	53	27	
Favorable reports	5	31	
versus			32.4 ****
All other reports	90	44	
Unfavorable reports	53	27	
versus			6.4 **
All other reports	42	48	

**** $p < .001$
** $p < .025$

TABLE VI

BEHAVIORAL ITEMS – BOYS

(corrected scores)

Item		CM+	CM-	x^2
Motivation	good	5	19	15.9 ****
	poor	29	11	
Attention span	long	0	16	1.5 #
	short	1	11	
Work habits	good	0	20	11.6 ****
	poor	7	8	
"Maturity"	mature	1	9	4.7 *
	immature	12	12	
Peer relations	good	0	1	2.6 #
	poor	13	4	
Coordination	good	2	6	9.2 ***
	poor	11	1	
				Binomial Test
Cooperation		0	8	***
Hyperactivity		1	0	#
Psycho-neurological problems		25	11	#
Underachievement		11	4	#
Speech – hearing problems		11	1	***
Referred for psychiatric treatment or remedial teaching		15	6	#
Receiving some psychological help		12	2	**

**** $p < .001$
*** $p < .01$
** $p < .025$
* $p < .05$
# not significant

TABLE VII

SPECIFIC ACADEMIC RATINGS – GIRLS

Subject		CM+	CM-	
Reading	good	0	3	☐
	poor	2	1	
Mathematics	good	0	3	☐
	poor	0	8	
Language	good	0	2	☐
	poor	0	1	
Spelling	good	0	3	☐
	poor	2	2	
Writing	good	0	2	☐
	poor	1	1	

☐ sample not large enough to make results meaningful

TABLE VIII

CUMULATIVE BEHAVIORAL RATING – GIRLS

Girls	CM+	CM-	x^2
Favorable reports	4	16	
versus			8.1 **
Unfavorable reports	9	4	
Favorable reports	4	16	
versus			12.0 ***
All other reports	21	9	
Unfavorable reports	9	4	
versus			2.6 #
All other reports	16	21	

*** $p < .01$
** $p < .025$
# not significant

TABLE IX

BEHAVIORAL ITEMS – GIRLS

Item		CM+	CM-	x^2
Motivation	good	5	5	1.9 #
	poor	10	3	
Attention span	long	0	0	*** (by Binomial)
	short	11	1	
Work habits	good	0	8	10.0 ☐
	poor	2	0	
"Maturity"	mature	0	7	*** (by Binomial)
	immature	0	0	
Peer relations	good	0	3	☐
	poor	0	0	
Coordination	good	0	3	☐
	poor	1	0	
				Binomial Test
Cooperation		0	8	***
Hyperactivity		1	0	#
Psycho-neurological problems		2	2	#
Underachievement		3	0	#
Speech – hearing problems		0	1	#
Referred for psychiatric treatment or remedial teaching		3	1	#
Receiving some psychological help		0	1	#

*** $p < .01$
# not significant
☐ sample not large enough to make results meaningful

TABLE X

TAPPING PERFORMANCE OF DELINQUENTS

	TWO HANDS TOGETHER		TWO HANDS ALTERNATING		FAST RATE DOMINANT HAND	
	Mean rate / second one hand	t value	Mean rate / second one hand	t value	Mean rate / second dom. hand	t value
BOYS						
CM+	2.37	7.98 ****	1.66	5.27 ****	4.98	1.50 #
CM-	4.27		2.81		5.21	
GIRLS						
CM+	3.24	3.65 *	2.25	2.13 *	4.99	1.11 #
CM-	2.95		2.03		4.52	

**** $p < .001$
* $p < .05$
# not significant

THE DEVELOPMENT OF SKELETAL MALFORMATIONS

Arthur M. Pappas, M.D.

Acting Chief of Orthopedic Surgery
The Children's Hospital Medical Center
Boston, Mass.

An infant with a severe congenital malformation of the musculoskeletal system represents the greatest challenge in reconstructive pediatric orthopedic surgery. When an orthopedist examines a child with a severe malformation of the musculoskeletal system, he must plan a complex long-term program that will result in the best possible function for the child at the termination of his growth. This goal must be achieved through a minimum number of carefully planned surgical procedures, as unnecessary scarring, alteration of neurovascular patterns, and the effect of growth can result in an overall loss rather than the desired improvement.

If such malformations are to be treated effectively, the underlying aberrations of embryological development and the subsequent related anatomical changes must be completely understood. The x-ray characteristics of certain skeletal abnormalities reveal obvious areas of deficiency, duplication, fusion, or arrest. (Figure 1) The apparent skeletal defect may be the primary malformation; however, in many instances, there is an associated abnormality of other neuromusculoskeletal components which can be of major importance in the overall assessment of the malformation and the long range planning for its reconstruction.

If we are to apply the progress of research efforts in the biomedical-engineering fields to the reconstruction of malformations of the musculoskeletal system, we must have the basic knowledge of underlying intracellular and intercellular vagaries of abnormal embryogenesis and their later expression as abnormalities of functional anatomy.

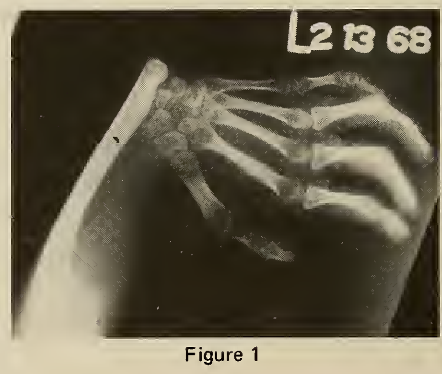

Figure 1

Our concern for excellence in the reconstruction of congenital defects reflects our society's compassion for these individuals. Such compassion has not always existed. During ancient times individuals with embryogenic abnormalities were thought to be endowed with supernatural physical and spiritual abilities, and, in some instances, were the focus of certain religious beliefs. During the middle ages this philosophy was reversed and individuals with congenital malformations were looked upon with disdain, often to the point of ostracism. The reasons for the malformations frequently were considered to be unusual celestial occurrences, interference by the devil, witchcraft, abnormal spirits possessed by either the mother or the father, unusual events during pregnancy, retribution for sins, or hybridity. Some of these impressions outlasted the middle ages. Within the history of this country, individuals have been tried and prosecuted for their alleged guilt in producing congenitally malformed offspring either through hybridity or as retribution for sinful living. It has only been within the last few decades that congenital malformations have been associated with such causes as rubella (German measles virus) and thalidomide, the drug that presented a woeful array of severe musculoskeletal malformations. Recent scientific reports have led to a higher level of awareness of induced malformations and to a better understanding of their causes and various components.

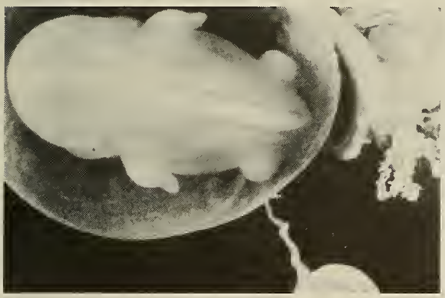
Figure 2

One cannot discuss teratology, the aberrations of developmental biology, without first having a background of normal embryogenesis of the skeletal system. The first evidence of limb bud formation of the human skeletal system occurs at approximately four weeks of development. (Figure 2) At this stage the embryo has advanced development of its central neural components. The limb buds demonstrate two basic types of cells to histological examination; the apical ectodermal ridge which outlines the periphery of the bud and the central mass of undifferentiated primitive mesenchymal cells. These central messenchymal cells appear to be identical; however, they possess a variable biochemical structure that is most important in the subsequent programming of limb development. The intracellular anatomical and biochemical ultrastructures present changes that actually precede the histological identification of cell change by three to four days. For example, using sulphur 35 as a metabolic tag, we are able to identify cells within this apparently undifferentiated mass that are destined to become cartilage and bone cells 72 to 96 hours before they show the histological characteristics that we usually ascribe to such cells. (Figure 3)

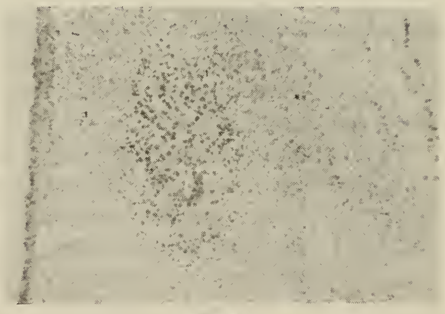
Figure 3

The role of reciprocal cellular and extracellular matrix interactions during the early stages of embryogenesis is undoubtedly of great importance in the early inductive sequences of skeletal morphogenesis. Recent biochemical evidence corroborates the essential relationship of embryonic cellular associations and aggregations in the determination of subsequent competence of cellular and metabolic differentiation.

As the limb development proceeds through its various biochemical steps, the precartilage anlage of the bone are identifiable. These are the first identifiable structures in limb formation. Following a general pattern of proximal to distal formation, the bones form in a closely related sequence. In concert with and succeeding bone formation are the stages of joint formation and the muscle relationships come into focus. (Figure 4)

Thus, in the overall formation of the human limb, the limb bud is first evident at approximately four weeks. During the next three to four weeks the entire differentiated limb will form. Any changes between eight weeks of development and forty weeks when the infant is born are basically changes of maturation and growth.

Figure 4

In our attempt to study experimental congenital malformations of the skeletal system, we have used a number of agents to induce the malformations. These include hormones, drugs, radiation, viruses, and immunologic alterations. Virtually all known drugs, chemicals, and physical measures administered in the proper dosage at a susceptible developmental stage of cell activity have the potential to induce changes of the developmental patterns of skeletal tissue. In general, these malformations are most likely to occur if the teratogenic agents are introduced during the critical developmental pattern of rapid chemical and morphological maturation. It is the effect of drugs during the stages of rapid cell differentiation that has brought the field of teratology into very close relationship with the field of oncology. The drugs used in the treatment of certain forms of cancer have proven to be effective in the production of experimental malformations in animals. As one would expect, the maximum effect of these drugs is on the most active metabolic and rapidly differentiating cells of the limb, thus determining the individual susceptibility of the different structures.

The drug that we have found to be particularly effective in producing malformations of the musculoskeletal system is myleran. Myleran is an alkylating agent frequently used for inhibition of rapidly dividing cells in certain forms of leukemia. We have observed that by injecting myleran into small mammals at known stages of their pregnancy, it is possible to produce an entire spectrum of abnormalities that very closely follow the patterns of limb embryogenesis and range from defects in vertebral development to absence of long bones, failure of joint formation, syndactyly, and polydactyly.

The earliest stage when embryos will survive exposure to this particular drug yet develop secondary abnormalities of the skeletal system is just before the limb bud first appears and when actual differentiation of the skull, spinal column, and scapula are occurring. Exposure during this phase results in malformations of the skull, the shoulder girdle, the spinal column, and ribs. The spinal column changes can be seen as absent vertebral bodies, partial vertebral bodies, and fusions of segments. (Figure 5) There are multiple areas of rib fusions. As development progresses, abnormalities are observed in the forelimb as shortening of the radius, absence of the ulna, and in the hind limb as defects of the tibia, and, approximately two or three days later, as defects of the paws.

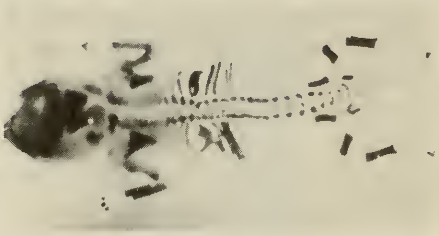
Figure 5

Defects of the paws are noted as duplications of digits, failure of development of digits, and, in certain instances, marked overgrowth of digits.

The histological findings related to these malformations usually revealed a normal limb bud without any change for approximately 48 hours, whereas alteration of S^{35} autoradiographs precedes the cellular changes. The cells appear quite abnormal in their staining characteristics and later exhibit altered intra- and intercellular relationships with large areas of vacuolization and later marked disorganization of total limb formation. (Figure 6)

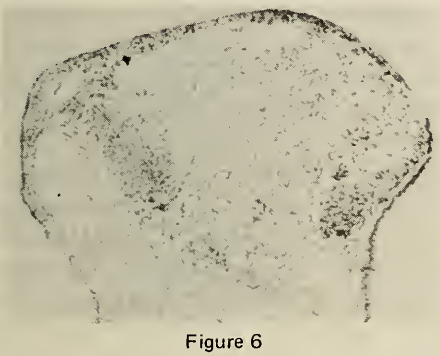
Figure 6

From our investigations it is clear that the spectrum of abnormalities produced by injection of myleran into pregnant rats was related to the time of administration in a highly specific fashion. This implies a time dependent differential susceptibility of embryogenesis, such that one portion of the embryo can be selectively damaged while other parts remain intact. From the types of anomalies we have induced, definite clues may be derived concerning the morphogenetic mechanisms involved in aberrant embryological development. As the early limb primordium develops through a series of normal inductive interactions, ablation of a single cell or a group of cells can cause deficiency or hypoplasia of a limb component. We are uncertain as to the specific effect of myleran on rapidly proliferating cells. Studies suggest myleran acts by cross-linking bases in the DNA, inhibiting its replication and continued limb development. The application of this information to explain the teratogenic effect of myleran is unproved; however, it does provide an appealing hypothesis. It is clear that the specific toxicity of the drug and the time dependent susceptibility of the tissues interact to determine the nature of the deformity. In most of the myleran induced malformations, anlage of the damaged structures was not microscopically detectable at the time of the injury. Therefore, it is evident that myleran exerts its effect not on the specific tissue affected but on the precursor cells, in some way blocking the inductive system. Therefore, cellular differentiation at the biochemical level must antedate that of the microscopic level. It is this phase that we are pursuing, using sulphur 35 as a metabolic tag. Sulphur 35 accumulates in the precartilaginous area of limb buds, suggesting that sulphate synthesis has begun before any other evidence of the cartilaginous anlage can be recognized. Therefore, this is a reasonable method to define the cartilaginous areas at the biochemical point of differentiation rather than waiting for microscopic differentiation. Presumably as the cells damaged by myleran are passing through this stage at maximum sensitivity, there is a metabolic block that results in an interruption of biochemical differentiation of the limb. As limb development proceeds, the system of reciprocal induction of paddle or paw formation and its relationship to the more proximal portions of the limb proves another most interesting area for evaluation. The interaction of this embryological paddle and the proximal limb segments is not well understood. It is becoming more evident that the paddle does have its basic influence on the carpal, metacarpal and phalangeal development. However, this is not an independent role as defects occurring at a more proximal level can interrupt the reciprocal inductive influences, thereby deleting certain aspects of the limb that the paddle is usually responsible for, whereas excision of portions of the paddle will result in deficiencies of the hand where normal development is occurring proximal to it.

The effect of a teratogen on the developing embryo is demonstrable by specific gross anatomic alterations. However, the initial alteration of the developmental process through translation of nucleic acid programs, intermediate metabolic pathways, and the ribosome, lysosome, or other structure systems must affect specific tissue inductive systems and interruption of any of these interdependent systems results in arrests or alterations of the morphogenetive process. Before final deductions about the unanswered problems of normal embryogenesis and teratogenesis can be postulated, the individual and coordinative sequences mediated through these processes must be investigated in more detail.

In our continuing search for the most effective methods for treating congenitally malformed children, we are developing investigative programs to define the early defects of embryogenesis that result in skeletal abnormalities. It is of basic and applied significance for us to understand and be able to predict what neuromuscular structures are present and are absent with each different extremity malformation. This information is vital for the planning of reconstructive and rehabilitative procedures. As we progress in the field of transplantation and electronic instrumentation, it will be important to know if the structures present in malformed limbs are of normal biochemical and physiologic structure and function – for example, whether the nerves leading to a congenitally abnormal extremity can carry the necessary impulses from the brain to activate transplanted or electronically controlled artificial limb components. (Figure 7) This young lady with bilateral amelia does have normal shoulder girdle function which implies normal neuromuscular control from the usual components of the brachial plexus. Whether or not the neuromuscular functions of the brachial plexus in their central development carry the potential for motivating more distal motor functions is unknown. There is greater likelihood for a child such as the one in Figure 8 to have at least part of the neuromuscular components in the malformed extremity. However, it is unknown which structures are absent and how they relate to the skeletal deficiencies and to the overall functional impairment and possible reconstructive procedures. By coordinating our data with those of others in allied biophysical medical fields, we hope to use information gained through our laboratory investigations to develop better methods for both surgical correction of lower extremity malformations and the development of artificial limb components to assist children with deficiencies and malformations of the musculoskeletal system, thus providing the necessary care which these children need and deserve.

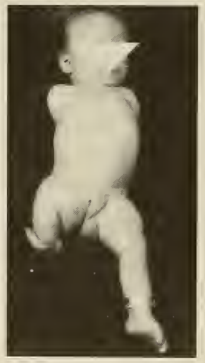

Figure 7

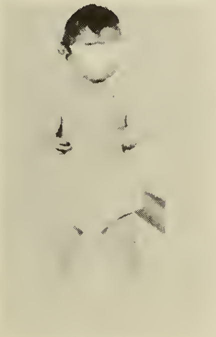

Figure 8

Bibliography

DiPAOLO, J.A., and KOTIN, P.: Teratogenesis--oncogenesis: A study of possible relationships. *Arch. Path.,* 81:3-23, 1966.

GREGG, N.M.: Congenital cataract following German measles in motherhood. *Tr. Ophth. Soc. Australia,* 3:35-46, 1941.

LANDAUER, W.: Hybridization between animals and man as a cause of congenital malformations. *Arch. Anat. (Strasb.),* 44(Supp.):153-164, 1961.

MELLIN, G.W., and KATZENSTEIN, M.: The sage of thalidomide. *New Eng. J. Med.,* **267**:1184-1193, 1238-1244, 1962.

PAPPAS, Arthur M.: Experimental congenital malformations of the motorskeletal system. *Clin. Ortho. & Relat. Res.*, No. 59, pp. 249-276, 1968.

SCHWARTZ, H., and PAPPAS, A.M.: Localization of S^{35} in developing embryos with myleran induced abnormalities. (In progress)

STREETER, G.L.: Developmental horizons in human embryos. IV. A review of the histogenesis of cartilage and bone. *Contr. Embryol. Carn. Inst.*, 33:151-168, 1949.

WEINGARTEN, P.L., REAM, J.K., and PAPPAS, A.M.: Extremity and digital malformations following injections of myleran. (Submitted for publication)

THE GROWTH AND DEVELOPMENT OF AN EXPERIMENTAL INTRACARDIAC INSTRUMENT

Walter J. Gamble, M.D.

Associate in Cardiology
The Children's Hospital Medical Center

One needs to answer the question, "Why look into hearts," before embarking on a program to develop an instrument that would enable one to inspect the inside of the heart without the need for major surgery. It has become ever more evident as great strides are made in cardiac surgery here, starting with the work of Robert Gross, that an accurate diagnosis is required prior to surgery. As the surgeons delve deeper into the heart, we as diagnosticians, must be able to tell them more accurately what they must find. An illustration of this is found in congenital aortic stenosis. If three cusps are present in the aortic valve, then the surgeon can expect to relieve the stenosis, as opening the three commissures will allow the leaflets to fall back during ventricular ejection. On the other hand, if only two cusps are present, then opening these will not greatly relieve the stenosis, as the two cusps act somewhat like bowstrings and cannot fall back during ventricular ejection. Unfortunately, good angiocardiograms usually do not allow us to count the cusps with the degree of certainty that we would like. Therefore, an inspection of the valve would be expected to give us the much needed answer. Another diagnostic problem is frequently encountered when tricuspid regurgitation complicates a septal defect. Here, the well-oxygenated blood crosses over from the left side of the heart, and may appear almost simultaneously in the right ventricle as well as in the right atrium. Did it come across a ventricular septal defect, then regurgitate into the atrium? Or did it cross directly through an atrial septal defect? A second shunt lesion where it is expected that visualization will be of great use is in differentiating some large flow patent ductuses from aortico-pulmonary windows. The catheterization data may be the same for both lesions. The angiograms may not be able to clearly show the site of shunt due to the rapid dilution and movement of the contrast material. In both of these two shunt lesions, one should be able to see where the bright blood comes from, as well as the actual lesion.

Conventional endoscopes are both rigid and usually of such a diameter as to prevent their being inserted into most blood vessels outside the chest. There is also the difficulty that opaque blood overlies all the intracardiac surfaces and gets in the way of good viewing. Let us trace how we attempted to solve these problems.

During the latter part of my training in cardiology here under Dr. Nadas, I read about fiberoptics, and learned that they could transmit light and even images through tiny flexible glass fibers.

In the Cardiac Research Lab, under doctors Monroe and LaFarge, we tested the idea of inflating a latex balloon inside the heart. If this balloon were pressed against something it was noted that the blood was squeezed off of the surface so contacted. A literature search showed the Swedes had already done it with a rigid 7mm. instrument in dogs.

We selected to work with the American Optical Company because they were willing to work on the problem as a joint effort, rather than delivering the instrument which would meet some spelled out specifications. I was not confident that I could design a successful instrument on the first try, nor forsee all the possible problems. With the help of Dr. Wohl at the Harvard School of Public Health I began to make balloons. It soon became apparent that a simple balloon would not suffice. I then began embedding various threads and fibers into the walls of the balloons. The various fibers include nylon, silk, and finally, glass threads unravelled from glass fiber curtains at home. These seemed to work, so I obtained a small sample. The 2-pound sample contained something over 100-miles, enough for a few tries. I built up a natural latex balloon on a small mold, stuck on the fibers, and continued to build it up. This resulted in a nice, stiff, clear balloon.

A prototype instrument was made keeping the design as simple as possible. The shaft was stainless steel and the fiberoptic bundle was a simple, but stiff, fused bundle containing 70,000 fibers. Its stiffness prevented its use from conventional catheterization sites. However, its small diameter (3.6 mm.) permitted it to be inserted from the jugular vein as the Swedes had done. In addition, it fitted into the carotid artery and could reach the left side of the heart. Many lessons were learned. It was found that if the balloon breaks blood soon coats the lenses, etc. We therefore planned to separate the lens system from the inflation system. However, the system served its intended purpose well in that pictures were obtained of the aortic valve and other regions of the heart.

Based on the experience gained with the prototype, we then jointly designed a flexible instrument. This instrument proved to be successful, and we were able to see and count the cusps of the aortic valve. However, a number of problems were identified. It was found, for example that we could not see the center of the aortic valve when we used a femoral arterial insertion point. The catheter tended to straighten out and remain against the wall of the ascending aorta after rounding the aortic arch. What was needed was some sort of a device to actively flex the tip of the catheter and pull it away from the wall so that we could see the center of the aortic valve where the cusps might be counted.

The light was insufficient for all but the crudest photography. I had to force develop motion picture film to an equivalent film speed of ASA 1500 using the fastest available black and white 8 mm. movie film.

Back in the laboratory we tackled the active flexion problem, testing out the various available flexion systems. Most involved use of the lumen of the cathetor, where the forces generated would crush the glass fibers with the catheter. Using crude materials we developed a system where we buried a fine wire within the wall of a catheter. A pull on the wire shortened that side of the catheter, causing it to bend. A trip to the U.S. Catheter Co., and talks with their engineers resulted in the production of a catheter. However, after all the optics were built in, the catheter cracked during its first use. We had placed too many stresses at a single point along the catheter sheath. This time the catheter company came up with a new design, and again the time-consuming installation of the optics was undertaken. A new illumination system, and a new handle to pull the wire were incorporated. The latter to prevent me from pulling too hard on the wire in my enthusiasm to bend the catheter a little more. Another unforeseen problem arose with the first couple of uses of the instrument. The extreme flexion caused wire threads in the catheter body to erode through the surface and break. A third attempt is now being undertaken to correct this deficit.

Where do we now stand? I am convinced that the mechanical problems I have described can be solved in the near future, and that we will be able to inspect diseased aortic valves. A right-angle viewing instrument which has been under concurrent development is now ready for use in selected patients, that is inspection within the pulmonary artery to differentiate between a ductus and an aortico-pulmonary window. I feel it is also ready to explore for suspected tumors invading the right atrium. However, this system needs the active flexion system, I believe, before it should be used in an attempt to look at the atrial and ventricular septa.

None of this development would have been possible had it not been for the environment of the Children's Hospital, one of warm support and willingness to support such ideas which may superficially seem to be difficult, if not impossible. People such as I have mentioned cannot be found at the drop of a hat. An administration and chief as Dr. Nadas are a necessity.

TUMOR AND ENDOTHELIUM:

NEW INVESTIGATIONS

M. Judah Folkman, M.D.

Surgeon-in-Chief
The Children's Hospital Medical Center

SUMMARY

We have shown that tumors grown in isolated perfused organs are prohibited from eliciting a new blood supply and because of this, fail to grow beyond a diameter of 3 millimeters. This implies that if we could block the ability of tumors to generate new blood supply in-vivo and thereby arrest growth at 3 millimeters, such tiny tumors might become extremely vulnerable to present methods of chemotherapy or future forms of immunotherapy.

In present investigations we are attempting to find out how tumors generate new capillaries and to isolate a humoral substance which may be responsible for this.

PREVIOUS WORK IN OUR LABORATORY

Experiments with isolated perfused organs first alerted us to the fact that tumors inhibited from generating new blood supply, arrested their growth. Over the past four years, thyroid glands from dogs and rabbits have been perfused in isolated chambers with small pumps and silicone oxygenators for periods of one or two weeks. Tumors such as melanoma and sarcoma implanted into these organs stop growing after they reach a diameter of 3 mm. They are unable to stimulate a blood supply from the organ and they appear to live by diffusion of nutrients from their local environment. When these tumors were re-implanted into mice, they rapidly stimulated new blood vessels and grew to a very large size. It was not clear what was missing from the isolated organ system which made tumor unable to attract blood vessels, but the relationship between absence of tumor angiogenesis and arrest of tumor growth was plain. Therefore, we began a study of the mechanism of tumor angiogenesis.

PREVIOUS WORK BY OTHER INVESTIGATORS

Sandison[1] first described a chamber implanted in the rabbit ear which he used for observing blood vessel growth under the microscope. Since then many workers have used a modification of this technique to study blood vessels growing into tumors. Warren and Shubik[2] have done extensive work. Shortly after implantation of live tumor cells neighboring capillaries contain endothelial cells in preparation for mitosis. By the second day, solid sprouts of new capillaries grow toward the tumor. They become hollow, fill with stagnant blood and leak plasma. By the third day they reach the tumor and connect with each other. Blood then streams into the tumor and rapid growth begins. Algire long ago pointed out that perhaps the single most important difference between benign and malignant tissue was this ability of malignant tissue to continuously elicit new capillary endothelium.

Although this process has often been described, no one had suggested a possible mechanism until recently, when Greenblatt and Shubik[3] pointed out that growing tumors might manufacture a diffusible or humoral substance which can stimulate the growth of new capillaries. They drew this conclusion from experiments with the Hamster cheek pouch, in which tumors enclosed within millipore filters were still able to stimulate capillary growth on the other side of the filter. Holes in the filter were small enough (0.4 microns) that no cells could pass, implying that some substance coming from the tumor must have diffused through the filter to stimulate the capillaries.

We have confirmed these experiments using millipore filters placed beneath the skin of rats in which large air sacs were previously made so that only one side of the filter is exposed to tissue.

PRESENT STUDIES IN OUR LABORATORY: FUTURE PLANS

If such a substance is present we would have to isolate it before we could ever learn to inhibit or destroy it. Isolation of such a substance from large amounts of tumor or tumor extract requires a suitable assay method. The millipore experiment indicates that a diffusible material is present but cannot be used as a quantitative assay to distinguish between active and inactive fractions of tumor extracts.

We are developing a quantitative assay system. It is based upon the assumption that whatever the tumor substance, it seems to effect endothelial cells specifically, i.e., those cells which form the lining of capillaries. Under ordinary conditions these cells rarely divide or undergo mitosis, except briefly to heal a wound. But in the presence of tumor, endothelial cells undergo vigorous mitotic activity. We have developed a new method of short term culture of endothelial cells (2-3 days) so that they can be exposed in-vitro to various tumor extracts and cell fractions. Mitotic figures which appear in these endothelial cells after exposure to the tumor material, are counted directly with a silver stain or indirectly by determination of DNA synthesis with tritiated thymidine incorporation. The number of mitotic figures indicates the activity of the tumor material which is being tested. A segment of rabbit jugular vein is used as a monolayer culture of endothelial cells. The vein is kept alive in a small test-tube size perfusion chamber. Once the assay is standardized so that a quantitative increase in mitotic activity is correlated with actively growing tumor, we will then be in a position to pursue the isolation of the factor responsible for stimulation of capillary growth.

Any guess as to the nature of this substance is speculative, but speculation is important to clarify the direction of these investigations. For working purposes we call this substance T.E.M. or tumor-endothelial message; if it can be isolated, it may possibly be inhibited by antibody made against it. Such an antibody might be used to arrest tumor growth at the 3 mm. limit. This could be a major form of therapy for tumors which rarely metastiasize such as brain tumors, and a powerful adjuvant therapy for other kinds of solid tumors.

This entire approach of attacking tumors by turning off angiogenesis is a different way of looking at tumor therapy, but one which may become valuable in future years as our ability to diagnose cancer is refined. Recent advances such as immunoassay of tumor antigens, would suggest that in the future patients may be treated with chemotherapy or immunotherapy because of a positive "test" for cancer long before the exact location of the tumor can be determined. Treatment might be continued until the test became negative.

A drug or antibody which would stop angiogenesis and, therefore, arrest tumor growth at 3 millimeters would make these tiny tumors very vulnerable to almost any method of chemotherapy or immunotherapy.

BIBLIOGRAPHY

1. American Journal of Anatomy 41:475, 1918.

2. Laboratory Investigation 15:464, 1966.

3. Journal of the National Cancer Institute 41:111, 1968.

THE NEXT TWO DECADES:

WILL CHILDREN'S

DUAL ROLE CHANGE?

Leonard W. Cronkhite, Jr., M.D.

General Director
The Children's Hospital Medical Center

On the occasion of one's 100th birthday, it is a permissible indulgence to speculate on the future course of events, and my perception at the moment must be less scientific in the field of basic research, and more related to the view point of the job that I now hold. I think 1969 is a particularly appropriate year for this exercise since the nation's health services are in a state of uneasiness, self-examination and concern. Even the most conservative individuals in the health field perceive, sometimes dimly to be sure, that health services cannot be selectively offered to a small portion of the population on the basis of affluence or geographic location. It is clear that the system is now expected to provide health services for an entire population.

While there has been a tendency to acknowledge to the existence of this basic premise, very little can be seen right now which would indicate that present methods of health care will be altered sufficiently so these ends can be accomplished. Our government has consistently identified target populations with great needs and has naively felt that solutions lie in massive expenditures of public funds. Clearly, this simplistic approach has not solved the problem. Let us look for a moment to a number of basic issues which we here at Children's Hospital must contemplate during this next several decades.

Biological Outcome

The first has to do with biological outcome which is a phrase now widely used in Washington. We have all seen health programs designed to improve the quality of life, which have been initiated at tremendous costs, but with virtually no measurement or attempted measurement of the biological outcome of such efforts. We find that we are extraordinarily lacking in precise measurements which will tell us whether or not what we have done for people has, in fact, been good for them. We find embarrassing questions being asked, such as "Does the establishment of a store front clinic in the core city materially affect the health and welfare of its clientele?" If we claim that it does, how can we prove it to legislatures less enamored of the idea than ourselves? What parameters can be measured to indicate that a change in the biological well-being of a human being is actually taking place? Can several health delivery systems be compared one with the other in a critical scientific fashion? We have virtually no knowledge in this field, though we have such firm convictions about the efficacy of our labors that the rhetoric sometimes becomes deafening. One small hope on the horizon has been the establishment of the National Center for Health Services Research and Development and its numerous sub-centers based at the universities, of which Harvard is blessed with one. Clearly, in the future every hospital will have a small cluster of scientists whose field is neither clinical nor basic research in traditional form but who have been trained to do research on the health delivery system. These individuals will be a diverse lot; they will have their origins in medicine, economics, statistics, public administration, law and sociology. It makes no sense whatsoever to plan programs to expend millions of dollars without looking at the biological outcome with the same scientific precision that we apply to medicine and molecular biology.

Redistribution of Tasks

The second general area of concern has to do with the redistribution of tasks in our health system. Those who have analyzed the availability of health manpower of all categories universally predict an appalling shortage of personnel in this next decade which raises serious questions about the ability of the system to deliver medical care to an entire population. I personally cannot but agree that if the distribution of medical tasks remains in its present fixed form, the job cannot be done. While many thoughtful individuals acknowledge these realities, there are only a few pilot experiments going on to redistribute the tasks which collectively make up the elements of health care. Indeed there are powerful forces today which prevent any radical departure from the status quo. These forces range from statutory and legal constraints to the phenomenon of over-professionalism, to the jealousies and pride of professional organizations to the sociology of consumer acceptance. None the less, these efforts must be pursued vigorously in this next few decades before the health system is overwhelmed by its inability to deliver the requisite services. Perhaps at the present time the biggest confusion lies in trying to distinguish between general education for people in health and the acquisition of a specific skill. We still tend to put the two together and assume that if one can finally acquire a Ph.D. or some other exaulted degree, he will indeed, perforce, be a skillful worker. This is probably not so and if we maintain this level of credential fetish in an industry which will require from three to four million people, the job cannot be done.

Methods of Financing

Thirdly, the methods of financing are a major problem, especially for somebody in my position. The present methods of health care financing have an Alice-in-Wonderland quality which cause no small meriment when viewed by our colleagues from Europe or from Australia. Our characteristic fixation of putting a price tag on each element of medical care actually stands in the way of thinking of comprehensive health care. Even more striking is that this price tag fixation almost entirely eliminates the concepts of preventive medicine and health maintenance, since these are even more difficult to cost out. It's an expensive system, since all major health insitutions, including our own, employ hundreds of individuals whose sole task is to fix a price on the aspirin tablet, the urinalysis, or the appendectomy. None of these individuals, nor the health dollars they consume, contribute one single benefit to the nation's health. It is clear that we must move in the direction of some type of comprehensive prepaid health insurance, both voluntary and government, on a large scale which will erase our preoccupation with financial considerations.

The Public and the Private Sector

We have the problem that there are indeed at least two medical systems extant in the country today. The most obvious differentiation is between the private and the public health sector. Medical institutions such as ours have, by and large, had their origins in the conscience of private individuals, both physicians and laymen. As the institutions prospered and indeed contributed mightily to methods of care, teaching and science, they withdrew for a variety of reasons from certain functions. When this withdrawal occurred, the government often stepped in. So that we now see that there are federal, state, county and municipal governments which have assumed an operational responsibility for certain categories of patients in which the private institutions have either lost interest or could not afford to be involved with. We now find that the chronically mentally ill, the chronically physically ill, the poor minorities in the core city or in the rural areas, mariners, veterans, Indians, Eskimos and the like and many others of the less fortunate in our population are now a responsibility, from an operational standpoint, of government. Thus at the present time we have two independent operational entities in health care under different sponsorship and I must say tragically one not communicating with the other. Most medical statesmen today who have the temerity to inquire as to the respective role of government and the private sector have been told most often to mind their own business and not rock the boat. But these questions must be asked and the two broad categories of delivery systems must be weighed, evaluated and ultimately judged on a non-political basis.

Fifth, and perhaps the most troublesome because it's been with us so long, are the problems of achieving balance in an institution which has one foot in public welfare and the other foot in the world of academics. As I sit in my office there are three broad categories of supplicants who beat a path to my door.

One is a group of students and young faculty who come saying that the era of the teacher, the wise Mr. Chips is gone, and that teaching in an academically oriented hospital no longer takes place. The student says, "This is my life that you are toying with, I never see my seniors, the curriculum is irrelevant, the art of teaching for the development of the young is a lost phenomenon." They are frustrated, angry, and hostile. As I try to maintain some neutrality among these supplicants I must concede that there is more than a germ of truth to what they profess.

Another group is the scientists in our institution. Those whose lives as you have heard will be based in the laboratory, who tell me that the threat to their existence is clear, in that the budget for the health research establishment in government has been cut. They say that the trend seems to be going toward doing public service and getting the Hospital involved in community needs, that this will dissipate those few reserves we have, that, basic science investigation will suffer, and that there is a clear danger that we are becoming a service institution which will lose the scientific stature of the last 100 years; I have to concede that they too have a point.

There is another group who have, as most of us do these days by force, a rather hypertrophied social consciousness who say that the Hospital cannot exist in the splendid isolation of disinvolvement with what is going on in our community. They say that we have to "get out there and do something" for the poor, the disadvantaged, the Black, the Spanish speaking, the rural, the crippled, and so on. If we don't do this we won't survive and I must concede that they have a point also. So we really see dramatized in the microcosm of my office three points of view – service, basic science and teaching – which are the same three cornerstones of an institution like ours which have characterized us for 100 years. Each has its proponents, each is quite right. The problem is the same problem that's plagued us and plagued our trustees and our staff from the beginning. If we had unlimited resources there might be no problem. Since we have limited resources, the next question is, "What form should the goverance of institutions like ours take in the future?" Some of you if I pause long enough will hope I have an answer. Clearly I don't, but someone obviously has to maintain a reasonable balance among the aspirations of these three groups of people who perceive their life and their future in a different context. The only thing I am convinced of is that if you disturb the balance and there is not reasonable equity in distributing your assets toward teaching, and toward science, and toward public service that the institution will not prosper in future years. So as we look at the plans which we are now formulating for 1979, we find that we have this background of trying to achieve equity in the three major areas of concern and that we find surprisingly that we have very little knowledge of what the social and economic climate will be that year. We have seen such extraordinary changes in the past decades that our own predictions are suspect. It may well be that we find ourself in the process of planning now quite irrationally. I personally feel that predictions for the future of The Children's Hospital Medical Center, which are based entirely on logical projections of past events, is in itself an irrational act. There is a certain comforting logic, however, in planning on the basis of the way things are now. One studies population densities, birth rates, scientific discoveries, patient flow patterns, regionalization, method of finance and we inevitably will come up with a larger institution basically in the same mold as today. Yet one knows that this will not be the case at that juncture. We can only strive for maximum flexibility, a short response time, a spirit of inquiry, and a youthful outlook which will, as our students say, make us relevant in 1979.

THE NATION'S NURSING NEEDS:

FEDERAL GOVERNMENT RESPONDS

Jessie M. Scott, R.N.

Director, Division of Nursing,
United States Public Health Service

It is a pleasure for me to be with you today in celebration of the 100th anniversary of the Children's Hospital Medical Center and in observance of the 80th year of the Children's Hospital School of Nursing.

I can only marvel at the resiliency of the Hospital Center in withstanding a century of unending change and serious National crises.

It is difficult to believe that a hospital could respond so flexibly during 100 years – first to a rural, pioneer culture and then to a highly industrialized, over-crowded urban civilization. Of course the greatest changes have occurred in the last 15-20 years. This period has become as inflated as the American dollar. A generation of new knowledge and new technology has taken place every five years, and is now threatening to make a complete turnover every two years. It is little wonder that our youth feel that 30 is the beginning of middle age. And yet creative professional people above the advanced age of 30 must not only keep abreast of the times, but be far out front, if they are to contribute to their fields.

Nor is it surprising with a population nearing 200 million, predominantly young and increasingly well-educated, that the health professions have problems in keeping up-to-date. Our younger colleagues are producing floods of new information, new knowledge, and new technology. And more will follow.

Our younger colleagues believe that nursing problems cannot be solved by trial and error approaches but only through specific research after intensive education. Now they are concerned about the use of mechnaical equipment as part of basic nursing skills. How can technical nurses keep up with technical machines – and master them? How can nurses help patients to adjust to a mechanical environment? Will the nursing duties of tomorrow as envisioned by them be carried out by technically knowledgeable nurses or by medical engineers as part of the therapeutic team?

I think that we must never lose sight of the fact that the importance of individual schools of nursing has never been greater than in this era of rapid mobility and jetstar communication. Knowledge does not wait upon slow evolution or chance discovery of ideas but upon our deliberate willingness to share.

Nursing progress everywhere is shadowed by a common and critical problem: A severe shortage of professional nurses. Our need for those who teach and those who direct care, remains acute.

At no other time probably in the provision of health care and the development of knowledge about health have more stresses and strains and, simultaneously more golden opportunities, come together than now.

If the ultimate aim of nursing services indeed all health services is the preservation of the dignity of individuals, and I believe it is, then we must see ourselves as part of a whole. The person who wants to stay well, or the person who is ill is our reason for being and not our own interests, our own specialty and certainly not our own convenience. The day of the solitary research worker or the single handed physician or the single nurse providing every part of care has passed.

Only by involvement with others, with making relevant the efforts of those who provide health services can the array of skills, the depth and breadth of knowledge and the availability of the resources of us all be developed to achieve our aim of comprehensive and modern health care system.

It is paradoxical to speak about modern advances and yet realize that our models of contemporary nursing education arose in the late nineteenth and early twentieth centuries. Few fundamental changes have occurred in the organization of our schools and courses of study since then although course content has changed markedly. Interestingly enough the ways in which health services are provided are rather simple extensions of patterns and systems that are really older than education, health education. Our ways have been modified to reflect the entree of professionals to enhance their importance.

I would suggest to you that this is over. One very important – very significant factor is the change in social attitude. Health care has been given to the very rich and to the very poor. We have a long history in this country of caring for the sick poor, and for those who could pay for themselves. Now society believes that everybody should have care at the highest possible level of quality and that there shall be no financial barriers. This has led to health insurance and to legislation passed by the Congress to provide the resources to pay for care for people over 65 years of age (Medicare) and to provide for payment of care for those who could not otherwise have it (Medicaid).

Another facet to the constellation of problems and opportunities is education. Education is the foundation of our society. The significance of it remains unquestioned. The significance of it for every man and woman is a more recent acknowledgement. The old system of exclusion is giving way to a new demand, a new concept of expectation.

Where once education was thought to be primarily for those with greater economic means, for those of high birth and social class, we now find that this kind of education by exclusion is no longer acceptable nor suitable. Changes in concepts of *who* should be taught are accompanied by changes in ideas of *how* they should be taught, and for *what*.

Today's developments tell us that in the next decade concentration will be on distribution of health services and the people to provide them.

In this regard there are certain kinds of things the Federal government can do that smaller governmental units and single institutions cannot do. It can stimulate, help to redistribute resources, collect data on a national basis, interpret it and make it available so that throughout the country people can have basic information about comparable events, comparable programs, comparable needs, and possible solutions. This is essential to us in the government if we are to plan at all well, and it is, I believe, most helpful to local communities and agencies. Those of you who know us in the Division of Nursing know that this has formed the basis for much of our program.

I think that it should be recognized and early on, that we at the national level are not producers. Production takes place right here, locally, in the places where people live, where they learn, where they work and care for each other. This partnership works only if partners are equal and if each knows and accepts what the other does and does not do.

One of the things the Federal government does do is provide resources. The Nurse Training Act is, of course, the basic piece of legislation through which resources are made available to those who are in the profession of nursing and the education of nurses. It is, I believe, the most significant single piece of legislation enacted in the interest and support of nursing. The legislation concentrates on four different aspects of the educational process.

First, there is support for the individual interested in a career in nursing and who needs help to attain his goal. And there is also the traineeship program established to assist in the preparation of our leaders in nursing, particularly teachers. This need brought to the attention of the Congress more than a decade ago continues. We must encourage more people to come into this field. The heart of the matter lies in teachers. They are the seed for our future.

Secondly, is the construction of teaching facilities.

Thirdly, a major area of interest and support is the development of curriculum – the content, methodology, and technology –

A fourth major function provided for is research and education – for experiments in education, for demonstration projects. Added to this is the authority we already have for basic research in nursing.

I think that we can be excited with the tremendous revitalization and revelance that is going on in all types of nursing education programs. What schools are doing with grants awarded under the Nurse Training Act is especially impressive. The people responsible for nursing education have been quick to react to the fact that there is so much more to know and there are so many new ways to learn. They are producing dramatic changes that are accelerating the learning process, increasing the number of students that can be taught, and making curriculum more meaningful in relation to the responsibilities of modern day nursing.

It is my impression that the Nurse Training Act of 1964 has helped stimulate more progressive changes in nursing education and nursing practices than have occurred in any previous period. But in administering the Act, we in the Division of Nursing are perhaps too close to weigh these changes objectively. I will mention a few to let you each decide from your own experience.

First, to illustrate the climate of change, I would like to mention some of the projects underway:

New Type Practitioner

In the West, where the distances between cities are immense, any kind of health services are frequently absent in the more rural counties. To offset the lack of a physician in a poverty area of 4,800 square miles, in 1965 the University of Colorado, through its Schools of Medicine and Nursing, mounted a training and demonstration program whose ultimate aim is to provide improved health care to children in both urban and rural areas. This program was designed to prepare a new type of health professional, the "pediatric nurse practitioner." More specifically, well qualified public health nurses are being prepared to assume an expanded role in child health care through a program which provides (1) four months intensive training in theory and practice of pediatrics and 12-20 months field practice under the direction of senior faculty members of the University of Colorado Schools of Medicine and Nursing, and (2) opportunity to use newly acquired knowledge and practice newly acquired skills in pediatrics in organized community child health programs in medically depressed rural and urban areas, as well as in pediatrician's offices. This expanded role includes many aspects of practice now performed exclusively by pediatricians, including well child management, management of minor illnesses and handling of minor child guidance problems.

Following the 4 month training period at the University of Colorado Medical Center, the pediatric nurse practitioners establish field stations for child health. Here, they hold daily office hours, make home visits and participate in the follow-up care of their patients whom they have referred to other health facilities. Immunization clinics and well child conferences are scheduled in advance and patients seen by appointment. In addition, the pediatric nurse practitioners provide services to families with well or sick children upon referral by physicians, other agencies, or by self-referral. Functioning within the scope of the Professional Nurse Practice Act of the State of Colorado, the graduate of the training program is prepared "to furnish comprehensive well child care to children of all ages, to identify and appraise acute and chronic conditions and refer them to other facilities as indicated, and to evaluate and temporarily manage emergency situations until medical assistance is available. Project nurses increase their knowledge and skills in assessing the physical and psychosocial development of well children; study variations of growth patterns; learn to perform developmental tests and evaluative procedures, such as history taking, basic physical examinations and a limited number of laboratory procedures; counsel parents in child-rearing practices; and carry out immunizations."

Another Project regarding Practice was carried out at the University of Kansas Medical Center, again by the joint collaboration of members of the Schools of Medicine and Nursing. The focus was on the needs of female patients, age 50 and over, for comprehensive care that could be supplied by nurses in the outpatient clinic. All the patients suffered from chronic degenerative diseases or from psychophysiological disorders. They were given an initial medical work-up and then divided into two groups – one experimental, the other a control group. An overwhelming majority of the

> patients in an attitude survey rejected strongly the idea that a nurse could perform certain medical procedures for them. The experimental group, however, received all their care from the nurse (except when referral to the physician was necessary.) A year after the project began, a number of significant changes appeared in the experimental group, while no change was observed in the control group.
>
> The experimental group now accepted the nurse without question as the primary source of care, and showed a preference for her as well as greater satisfaction in the treatment. In addition, this group kept their appointments much better than the control group. The control group spent 47 percent more time waiting for care than the experimental group and paid an average of $29 more per patient over the treatment period.

One of the biggest problems that local, State and National governments face today is how to bring this or some other kind of health services to the people. Few doctors make house calls and visiting nurses bring home care to only a fraction of the people in cities and rural areas. Out-patient clinics and emergency rooms, as you know so well, are crowded with people waiting for hours. And they come only at times of crisis. Some medical centers are experimenting with establishing health units in slum areas to give families medical and nursing care they need on a continuous basis, but it is still too little and too scattered.

> *Another study* I want to mention was a 4-year demonstration project conducted at the Montefiore Hospital in the Bronx, New York City. It explored the effects of placing public health nurses into obstetric and pediatric practice in association with a physician. Of particular interest was how the patients and the physicians would accept the enlarged activities of the nurse in providing continuity of care for mothers through the prenatal period and of both mother and infant for two years postpartum. Although only interim findings have been reported, they show that patients and physicians alike have accepted the nurse. The working relationships between nurses and physicians have gradually changed from hesitancy or unwillingness to active cooperation and confidence in each other's abilities. And since the nurses took over the entire responsibility for the home visits, they found their uses of their knowledge of nursing, medicine, sociology, and psychology particularly satisfying.

In recognition of the problem, more schools of nursing are emphasizing public health nursing in their curriculums. Faculties believe that hospital experiences do not give their students enough experience in view of the need for changing the delivery of health care in out-of-the-hospital nursing services. One diploma school in Texas is teaching the fundamentals of out of the hospital nursing by having each nurse choose a family from the clinic to help with monthly visits.

> Boston College was awarded a project grant to develop – not local – but regional clinical experience in public health nursing. The regional area is

within a 5-mile radius of Brockton, with an area population of 200,000. Since the project began, the faculty working with their students, have been able to develop permanent public health agencies to provide the nursing services this industrial area requires, while serving as a practice laboratory for the college.

The University of Arizona has a project grant to develop cultural components in public health nursing. The senior nursing students visit Papago Indian families on the San Xanvier Reservation, to learn to care for patients in a culture other than their own. A seminar in anthropology teaches the students to establish rapport with their assigned families in the hope of influencing favorably the Indian attitude toward good health practices. The students also learn to work with the medicine men, respecting their place in the culture. One medicine man does the diagnosis; a second handles the treatment; and a third gives the medicine. Shades of functional assignment – the students attend ceremonies, and learn above all else to consult with the Indians who want to be conferred with, not acted on.

These particular projects indicate how well schools of nursing are responding to their community needs. Generally the schools are (1) integrating public health studies throughout the curriculum; (2) giving students carefully selected intensive learning experiences; (3) exposing students early to out-of-hospital nursing care through family assignments; (4) using programs such as those sponsored by the Office of Economic Opportunity to give students experience in developing community health units; and (5) helping each student nurse, regardless of her choice of nursing field, to see her function as a member of a community health team.

I don't want to give you the impression that schools apply for curriculum grants to emphasize only public health nursing in their curriculums. Far from it. They are experimenting with all kinds of methods and materials to improve the teaching of nursing. A school in Florida is developing self-instructional materials in pediatric nursing. The materials include slides and synchronized slide-tape programs of nursing procedures used in the care of children. Other multi-media materials are single concept films, a programed text, and a text of programed pediatric nursing case presentations.

A Montana baccalaureate program has a grant to develop videotapes in the reorganization of its courses of study so that students on the campus at Great Falls can receive some instruction by its well-qualified faculty on the main campus at Billings.

Evanston Hospital in Illinois has a joint project with 17 other schools. The faculties of all 18 schools plan the production and telecasting of courses on general and nursing education subjects. Master teachers are used to conduct the classes, and the films are afterward available to other diploma schools of nursing. Part of the project is the evaluation of the limits and the potential of television for nursing education.

Another illustration of the use of technology in education is the Detroit Nursing Education Project Via 2500 MegaHertzian System Television. Here nursing students attending six diploma programs, 4 associate degree programs and 2 baccalaureate programs are taught simultaneously a common core of subject matter by master teachers via video tape. This project offers a remarkable instructional flexibility to the faculties of the various schools. The lectures and demonstrations can be taped for individual review of refresher training. They can be expanded upon by instructors whose students require more subject matter in depth. And they can introduce the techniques of this teaching adjunct to graduate students who are preparing to assume faculty positions. But most importantly, all students are exposed to the stimulation of the highest quality of teaching. And that, I believe, is excellent.

Five community colleges in New York are developing a large-scale tutoring service in an attempt to increase the students' rate of retention of the nursing subjects. Upper class students supply the tutoring according to the others' needs and prior preparation.

I could go on about the project grants, for they are exciting and stimulating. But I'm sure you can see how varied the projects are and how the needs of the faculties in teaching students from a particular area determine the subject of their study.

There have been fringe benefits to this program of curriculum grants that are almost more exciting than the improvements occurring in individual schools. I have been most impressed with the collaboration among schools of all types and with a faculty commitment, which is becoming evident, to good nursing education that takes precedence over commitment to an individual school.

Improving curriculum is only one area in which nursing education is forging ahead. New ways are being devised to recruit students, particularly young people from disadvantaged groups, and more important, to hold them there until graduation. Several schools are now undertaking remedial programs, and many community groups (as well as schools) are eager to begin.

We have negotiated two contracts, again made possible by Nurse Training Act monies, for identifying and encouraging students from minority groups and disadvantaged backgrounds. One provides funds to the ODWIN (i.e. open doors wider in nursing) project in Boston so that their activities, which include providing the essential tutorial assistance, can be expanded to reach more young people at an earlier age.

The second contract is with the ANA-NLN Nursing Career Committee. They will develop methods to demonstrate effective ways of motivating young people to enter and finish nursing programs. Materials will be developed suitable for use by counselors, community resource people and teachers.

In the construction grant program new schools are being built, old buildings are being renovated, additions are being constructed.

In applying for construction grants, faculties have found they had to plan more than classrooms, conference rooms, laboratories, faculty offices, libraries, or space for self-instruction or teaching by television. They have had to look at the area that the school serves – sometimes crossing State lines – to see the kind of nurses needed in the future in relationship to other schools. They have had to weigh the community field resources and hospital facilities available, and consider the areas that would contribute students in the future. This kind of cooperative planning has begun to eliminate the isolation and lack of collaborative effort that has characterized some schools of nursing.

We are also helping to develop clinical specialties throughout nursing research programs. For example, the research project conducted by Dr. Lawrence Meltzer and Miss Rose Pinneo at Presbyterian Hospital, University of Pennsylvania Medical Center in Philadelphia, will soon be available for specialty training of nurses in other hospitals and medical centers. It is a multimedia system of instruction to teach nurses to be totally responsible for patients suffering from infarction in intensive coronary care units. The nurse is the focus of the whole system. Nurses are instructed in the basic elements of electrocardiography and specifically in the identification of all arrhythmias – 30 in number. The nurses learn the chemical and mechanical treatment for each arrhythmia or other catastrophic situation. They proceed with lifesaving measures if the physician has not arrived within the crucial two minutes. This method has demonstrated that it can save the lives of 50 percent of the hospitalized heart patients since nurses do not have to wait helplessly while a doctor dashes from another area in the hospital.

Another teaching system that we hope to develop from a research project is the post-operative intensive care of the open-heart patient. This should be of great interest to you since I understand one child in 100 is born with one or more heart defects. And even without the risks of surgery, one-half to three-fourths of these children will die before their second birthdays.

A recent television drama that you may have seen centered on heart transplantation. The final moments of the show revealed the patient, after the successful operation, alone and serene in an empty room. His wife stood outside the glass wall of the room, waiting in his line of sight for him to open his eyes.

But after having seen hours of videotapes of 23 patients recovering from various kinds of open-heart surgery in Ohio State University Hospital, I marveled at the TV film. At Ohio, the post-operative patient lies surrounded in a tangle of wires to monitoring devices, drainage and suction tubes, oxygen tent and tubes, IV tubes, bottles, drugs and defibrilator paddle. The nurse works in a fury of concentrated efficiency to suction the patient to keep his air passages open. She makes him cough, she monitors his peripheral circulation, his renal sufficiency, his heart beat, his temperature, his blood pressure, and his electrolyte and acid-base balance. She is trying to restore all his natural functions that were in abeyance while he was on the heart-lung machine.

The contrast was marked between the TV show's quiet room, containing only the patient who might have had a slight headache and the real thing.

And the problem has been that these nurses, with only a little orientation, have had to extemporize only their own previous medical-surgical experience. We hope to produce a teaching system that will give them and others interested in heart surgery what they need to know about this complicated and specialized subject.

It is from this kind of nursing research that many of the new nursing specialties will come.

There are other kinds of financial aid for nurses and students under the Nurse Training Act that you are probably familiar with. The seminars and short-term traineeship courses for nurses are paid for with Nurse Training funds and sponsored by your nursing organizations, regional organizations such as New England Board of Higher Education or universities and other schools. There are nursing student loans and nursing scholarships. They are available to students enrolled, in all schools of nursing.

There are, of course, too many projects, too many programs to mention. Some are beginning, others are going forward, and some are nearing completion. Not all of them will produce a solid, gold nugget. But the ones that follow may. Research study is a good deal like panning for gold. There may be enough gleaming particles to lead us to a great and productive lode.

If I had to single out one area of accomplishment contributing most to nursing's forward movement, it would not be advances in nursing research; nor would it be growth and improvement in education. It would not even be demonstration of highest quality in patient care. Rather, it would be the growth in our ability to approach, through planning, the interrelatedness of all these together with improvements in society.

What is ahead for us – what are our prospects? The influence of individual nurses has never been greater than in our present mobile situation. As we go into the next decade I think we can expect greater emphasis on the expanded therapeutic role of the nurse (I do not mean physician assistant) and the nurse as the manager of care. Our educational and service institutions must provide the rationale, the know-how and the setting.

The final effectiveness is expressed in the individual served between individuals, and in the community.

Our continuity is in the person served – to this end we should bend our talents.

Thomas Wolfe has said that if a man has talent and does not use it he has failed. If he has talent and uses only some of it he has partly failed.

I wonder what would happen if all the skills and talents we have now, were to be used and used well.